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THE FUTURE OF ENZYME RESEARCH

The Fourth Edsel B. Ford Lecture, 1955

LINUS PAULING*

I am honored to have been invited to speak at this great International Symposium on Enzymes, and especially to be allowed to give a talk with the title The Future of Enzyme Research. This title suggests that I think that I know enough about the subject of enzymes to extrapolate its course into the future—I do not—or that I have a scientific crystal ball that I can look into—I do not. What I do have is a deep belief about the importance of enzymes as subjects for investigation, and a sincere admiration for enzyme chemists and biologists; and I am happy to be associated with them, even if only in the peripheral capacity of an after-dinner speaker.

The problem of enzymes encompasses essentially the whole of biology. When we understand enzymes—their structure, the mechanism of their synthesis, the mechanism of their action—we shall understand life, except for those aspects of life that involve mental processes; and I have no doubt that enzymes are important for these too.

Enzymes do an extraordinary job—that of causing chemical reactions to take place in the body, at body temperature, which without enzymes can be made to take place only under much different conditions or with great difficulty. The outstanding characteristic of enzymes is their specificity. For example, the enzyme β-galactosidase is able easily to hydrolyse a galactoside, whereas it has little effect on the hydrolysis of a glucoside, which differs from the galactoside only in the spatial configuration about a single carbon atom.

The specificity that is shown by enzymes in their activity is not unique to these substances. It is found also in the ability of antigens to produce specific antibodies, in the action of drugs and hormones, and in the action of genes in producing replicas of themselves and in serving also to produce other substances of well-defined structure. Of the various molecules that demonstrate specificity in their physiological activity, genes are the best. Antibodies are heterogeneous—they have the power of reacting not only with the antigen that caused their manufacture, but also with other antigens, more or less closely similar to the original one; enzymes may serve to catalyze reactions involving several different, somewhat related, substances; but genes seem to be nearly perfect in their action.

It is easy to understand why genes come closer to perfection than the other molecules with specific biological activity—there is an automatic mechanism for making genes better.[1] The manufacture of an antibody molecule is a process that occurs only once, so far as that molecule is concerned. I think that in the manufacture of an antibody molecule the antigen serves as the template, the antibody being molded about it. If the conditions under which the antibody molecule is being manufactured be such as to favor the formation of a good molecule, with high comple-

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*Director, Gates and Crellin Laboratories of Chemistry, California Institute of Technology. Read before the Henry Ford Hospital Medical Society, Nov. 1, 1955.

mentariness to the antigen molecule, the resulting molecule will be highly specific in its activity—it will be able to combine very strongly with the homologous antigen, and much less strongly with other molecules; but if conditions are unfavorable (including the operations of chance during the process of synthesis of the molecule) the antibody molecule that is formed may have only small power of combining with this antigen, and a greater power of combining with other molecules. There is no process of selection that operates to improve the quality of the antibody molecules that are manufactured with use of the injected antigen as the template. The process of duplication of genes is different in nature: it permits a search to be made for a molecular structure with improved power of reduplication. Let us consider, as an example, a gene that has undergone mutation. This molecule, which we may call A_1, serves as a template for the manufacture of a complementary molecule, B_1. This molecule, B_1, may then serve as the template for the manufacture of another molecule, A_2, complementary to B_1 and similar to A_1. By repetition of this process the series of molecules, each complementary to the preceding one, is continued: B_2, A_3, B_3, A_4, B_4, . . . If at any time in this process a molecule A_N happens to be formed that is perfectly suited to serving as the template in the two-stage manufacture of a duplicate of itself, the process of duplication from then on would be a perfectly reliable one. In this way, the mechanism of heredity permits the ultimate discovery of a gene with the power of duplicating itself perfectly; or perhaps of a gene with such a structure that the process of duplication, if not perfect, is quickly self-correcting.

In the above discussion we have assumed that biological specificity is the result of complementariness in structure, rather than identity in structure. Each of these two alternatives has its appeal. The idea that there are special forces that operate between identical molecules has been suggested to a number of investigators by the resonance phenomenon in quantum mechanics. It seems likely that the specific forces resulting from this phenomenon, operating between identical molecules, are so weak as to be negligible, in the case of large molecules such as proteins and nucleic acids.[2] There is no doubt whatever that the specificity of the interaction of antibodies and antigens is due to a detailed complementariness in surface configuration and structure that permits the antibody molecule and the antigen molecule to come into close contact (to within about 1 A of the minimum distance of approach) over a surface area approximately 100 A^2, and that the integrated weak forces of van der Waals attraction, coulomb attraction between positively charged and negatively charged groups, and hydrogen-bond formation between complementary hydrogen donors and acceptors leads to a specific bond of significant strength between the complementary molecules. I think that complementariness in molecular structure of the same sort is responsible for biological specificity in general. In particular, I think that it is likely that many enzymes—perhaps all enzymes except those involved in the transfer of electrons during oxidation-reduction reactions—are effective because of a complementariness in structure to the reacting molecules. By the "reacting molecules" I do not mean the substrate molecules themselves, with their normal configurations. If an enzyme were to have a structure complementary to that of the substrate molecules in their normal configurations, the combination of the substrate molecule with the enzyme would stabilize the system, and in this way would increase the energy of activation associated with the reaction, and hence decrease the speed of the reaction. If, however,

the enzyme were complementary in structure to the activated complex—the half-way structure in the chemical reaction—and not to the reactant molecules or the product molecules, then the energy of interaction of the enzyme with the activated complex would decrease the energy of activation, and hence increase the speed of the reaction. This is a reasonable picture of enzymic activity, and one that is supported by experimental information about inhibition of enzyme reactions. We see that a molecule of an excellent inhibitor of an enzyme is one that simulates in its structure the activated complex. By the continued study of inhibition of enzyme reactions and determination of the detailed molecular structure of the inhibitors it may be possible to reach some reliable and detailed conclusions about the structure of the enzyme itself, in the region carrying the activity.

In order to increase our knowledge of the structure and mechanism of action of enzymes more work must be done in the field of molecular structure. In particular, the present structure theory of chemistry, which applies in the main to substances in their normal states, must be extended to cover also the activated complexes. Because of the brief period of time during which the activated complexes exist, in the course of chemical reactions, the experimental study of their structure is difficult. I think that it is likely that the development of the field of structural chemistry of activated complexes will be made in large part through the application of theory—an extrapolation from the chemical structure theory of substances in their normal states.

Enzymology as a science now stands where organic chemistry stood a century ago, before the structural formulas of chemistry were developed. In the course of the many interesting papers about enzymes that were presented at the symposium today there was not shown a single lantern slide giving the interatomic interrelationships of an enzyme and the activated complex for the catalyzed reaction. The time is rapidly approaching when enzyme chemists will use structural formulas of activated complexes, and structural formulas of the enzymes with all interatomic dimensions correct; when this time comes, enzymology will have reached the stage in its development that has now been reached by organic chemistry.

Enzymes are proteins. During recent years we have seen the astounding development of chemical methods, including chromatography, to such power as to permit the determination of long sequences of amino acids in the polypeptide chains of proteins. It is evident, however, that an understanding of the specific properties of proteins cannot be obtained through knowledge of amino-acid sequences alone. It will also be necessary to have knowledge of the way in which the polypeptide chain is folded, and the detailed configuration in space of the side chains. I am confident that the x-ray investigation of crystals of globular proteins will be successful in leading to the complete structure determination—the location of every atom—of the molecules of many proteins long before the next fifty years of enzyme research is over. I am willing to forecast that within ten years there will have been made such a complete structure determination of at least one crystalline globular protein.

It is hard to forecast to how great an extent enzyme research during the next fifty years will lead to progress in the field of medicine. It is now known that a number of diseases are the result of some sort of abnormality involving enzymes, and

that perhaps these diseases should be described as molecular diseases, resulting from the synthesis of enzymes of abnormal structure, which are not able to carry out in a proper way the work that the enzyme normally does. Sickle cell anemia was the first disease to be recognized as resulting from the gene-controlled synthesis of an abnormal molecule, in this case the hemoglobin molecule. It has been shown that a condition that may be called a disease occurs in Neurospora as a result of the manufacture of abnormal molecules of the enzyme tryptophan synthetase. The disease phenylketonuria, which leads to mental deficiency and other manifestations, seems clearly to be the result of a gene-controlled failure of the individual to manufacture an effective enzyme that normally catalyzes the process of oxidation of phenylalanine to tyrosine. Perhaps the genic abnormality is such as to lead to a complete interruption of the process of manufacturing this enzyme, or perhaps an abnormal molecule is manufactured, which does not have the normal enzymic activity. A score of diseases have so far been recognized as enzyme diseases, presumably resulting from the manufacture of abnormal molecules in place of the active enzyme molecules. I think that it is not unlikely that there are hundreds or thousands of such diseases.

I foresee the day when many of these diseases will be treated by the use of artificial enzymes. When our understanding of enzyme activity becomes great enough, it will be possible to synthesize a catalyst for the oxidation of phenylalanine to tyrosine. A small amount of this catalyst may then be attached to a reticular framework inside of a small open-ended polythene tube, which can be permanently placed within an artery of a new-born child who has been shown by the presence of phenylpyruvic acid in the urine to have inherited phenylketonuria; through the action of the catalyst the child should then develop in a normal way. This idea seems fantastic now; but the world of 1955 is a fantastic world from the viewpoint of 1905, and I have little doubt that my prediction about the world of 2005 will turn out not to be a bold one, but rather a timid and unimaginative one.

Enzymes are wonderful substances—they consist of wonderful molecules. We do not know very much about these molecules as yet, and so far during this International Symposium on Enzymes there has been very little discussion of the new experimental information about enzymes in relation to the detailed molecular structures of the enzymes and the reacting molecules. I am sure that the field of enzyme research will be much different even fifteen years from now—that there will then be much greater knowledge than we now have of structure and activity of enzymes. I hope that fifteen years from now there will be another international symposium on enzymes here in Detroit, and that I may have the opportunity to attend it—and I predict that many of the speakers at this symposium, in 1970, will illustrate their papers by the use of slides showing detailed molecular structures of enzymes and reacting molecules.

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NEWER AGENTS FOR THE ANESTHESIOLOGIST*

PAUL R. DUMKE, M.D.**

At the time man began to look for agents which would produce pain relief and allow surgical procedures to be painless, he also became interested in methods of administering these agents. As we see our patients preoperatively most of them usually have two requests. First, they want to be "asleep" and second they want this "sleep" to be produced by an intravenous agent. Many specifically ask for pentothal. Some medical historians are already calling this present period "The Era of Intravenous Anesthesia."[1]

We have been interested in finding the safest anesthetic agent for the patient; one which gives the surgeon the best operative conditions and still is pleasant for induction and has no after effects. To date, no one agent meets these criterion. Needless to say, the perfection of an anesthesia does not lie in a drug alone. A great deal lies in the skill and artistry with which it is administered.

During the past 20 years we have been using intravenous agents more and more. Much has been learned about the metabolism of the ultra-rapid acting barbiturates. Brodie[2] and co-workers have shown that it is redistribution of these barbiturates which makes them ultra-short acting. Body fat, in this instance, acts as a reservoir in which the drug is stored and from there it is gradually released to be detoxicated relatively slowly by oxidation. The fat acts as a buffering mechanism which influences slightly the intensity of anesthesia, and much more the duration of anesthesia with these agents. The more fat there is in the body the more efficient is the buffering action, and the briefer the effect of a single injection of these agents. Recent work[3] has substantiated earlier evidence that the liver is the primary site of metabolism of these agents. Other tissues are quantitatively unimportant. Using thiopental containing S^{35} it has been shown that the breakdown of the molecule seems to be at the side chain. Oxidation of the side chain converts the molecule to a carboxylic acid derivative. This derivative has none of the central nervous depressant action of the parent drug. The metabolism of these ultra-short barbiturates is slow and with large doses or repeated small doses, the resulting plasma level equilibrium is above the anesthetic level and is maintained by the reservoir of fat. The post-anesthetic somnolence seen is due to persistance in the plasma of the bariturate itself which is coming out of the fat reservoir. This is the reason why unsupplemented use of these agents as anesthetics should be restricted to selected surgical operations of brief duration where only small doses are needed. It is safer to maintain the relatively stable barbiturate at a low plasma level for basal anesthesia, and to obtain depth of anesthesia with other agents when long surgical procedures are contemplated.

Because of the occasionally protracted period of somnolence and the tired weak feeling that some patients complain of due to the presence of the barbiturate in low concentration in the blood for 24-48 hours, the search goes on for other agents. One of these agents which is of interest and may have promise is hydroxydione (trade-name Viadril-Pfizer Lab.)

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*Given in part as a paper titled "Intravenous Anesthesia" to the Ontario Section of the Canadian Society of Anesthesiologists, Windsor, Ontario, Canada, 22 October, 1955.

**Physician-in-Charge, Division of Anesthesiology.

Selye[4] and others during their work in animals on hormone action noted depression and anesthesia with various steroids. Merryman[5] reported sleep in humans by the intravenous injection of progesterone. Recently[6] a group of water soluble steroids were tested for anesthetic activity. 21-hydroxy pregnanedione sodium succinate had the widest margin of safety, produced no hormonal effects, no salt retention, no pathological changes in organs but did produce anesthesia.[7] Figure 1 shows the relationship of hydroxydione, a water soluble steroid with anesthetic activity dissociated from the hormonal activity, to progesterone and also to hydrocortisone.

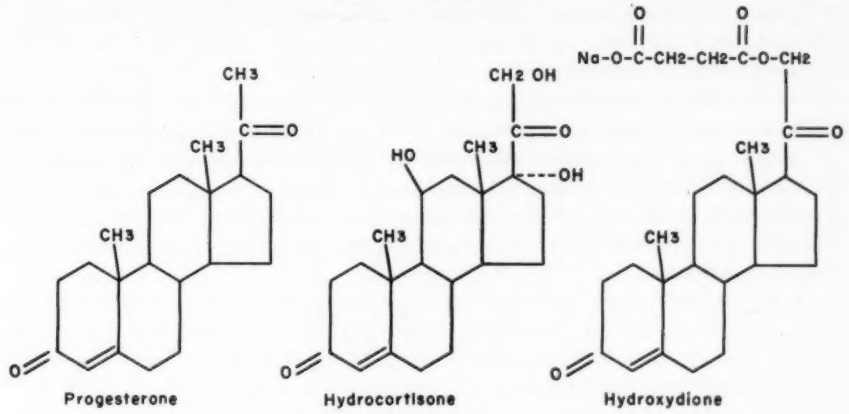


Figure 1

The relationship of hydroxydione to progesterone, and to cortisone.

It is structurally related to hormonally active steroids. This same configuration is similar to the substance in some of the tars which have been used to cause carcinoma in animals. It is a white crystalline material obtained as a free acid made water soluble by neutralization with sodium carbonate. Hydroxydione has been tested for estrogenic, androgenic, anabolic, progestational, corticoid, adrenal corticotrophic, thyrotropic and gonadotropic activities and these are absent. In animals and humans it effects cerebral metabolism like barbiturate anesthesia, namely reducing oxygen consumption of the brain when anesthesia is produced. The electroencephalographic picture is also quite similar to deep thiobarbiturate levels. When the drug is made up in 2.5 per cent solution it has a pH of 8.5-9.8 and direct injection into a vein causes pain and a high incidence of thrombosis. Injecting the drug slowly into an intravenous of 5 per cent glucose which is running rapidly has resulted in only mild burning of the arm in the occasional patient. With this technique the incidence of thrombosis or thrombophlebitis is no greater than when barbiturates are used.

Hydroxydione has definite anesthetic properties and its effects clinically are of interest. Injection of 0.5 to 1 gram intravenously produces unconsciousness in about 5 minutes and anesthesia in 7 to 10 minutes. There is practically no respiratory depression and little or no fall in blood pressure in the supine individual. No studies are reported of the effects of posture on the circulatory effects of the drug. The pulse rate remains unchanged with slow injection. With 0.5 gm. doses anesthesia lasts 30-45 minutes and on wakening patients appear wide awake, conscious and do not have the hangover effect produced by the barbiturates. The incidence of

nausea and vomiting has been remarkably low. Patients are pleased with its effect. The drug appears to produce some retrograde amnesia. In patients without the usual premedication of morphine or demerol and scopolamine there is retrograde amnesia of about 30 minutes.

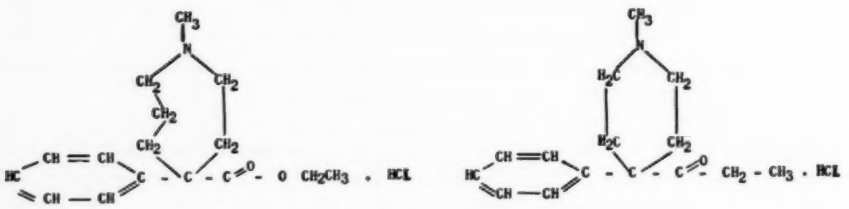
An interesting feature of this drug is the obtundation of the pharyngeal reflex. It is possible to expose the larynx with ease and without gagging or coughing in most patients who receive one gram of Viadril intravenously. The vocal cords are not however insensitive and will adduct if stimulated. They do not stay in spasm long and normal respiration occurs quite promptly. We use the drug to produce unconsciousness for suspension laryngoscopy and if the larynx is cocainized this method has proved very satisfactory.

As with barbiturates, if the anesthesia begins to wear off, more drug can be injected. The second dose is smaller and I am certain there is a cumulative effect.

Animal work with this drug has shown that hepatectomy and/or bilateral nephrectomy has no effect on duration of anesthesia or depth of anesthesia. The method of metabolism of the drug in the human has not been reported, but repeated daily anesthetic doses in monkeys has not shown any liver or kidney damage and no bone marrow depression.

Further evidence that the drug has anesthetic properties is that if meperidine is used to supplement it, as we usually do when we are using thiopental, much less meperidine is used than with the before mentioned drug. It produces a definite analgesic state far greater than that produced by barbiturates.

This latter property has given us an opportunity to use a new drug of the opiate series called heptacyclazine.[8] Heptacyclazine is an analog of meperidine. Figure 2 shows that it contains a seven numbered heterocyclic ring in place of piperidine in meperidine. To date, it has had modest clinical trials. Several properties are of interest. It definitely raises the pain threshold and is effective in treating clinical pain of postoperative patients. Its effectiveness seems to be somewhere between codeine and meperidine. The drug does not produce euphoria, sedation, amnesia or a sense of well being and thus differs from all the other opiates. Because of this, addiction to the drug is said to be absent. If this proves to be true it is the first opiate to have this property. Another interesting action is the lack of respiratory depression when this drug is given.



Heptacyclazine Meperidine hydrochloride

Figure 2
Formula of Heptacyclazine which is an analog of meperidine.

We have been using Viadril and heptacyclazine in combination and are pleased to have a patient with a pleasant and unexcited induction plus amnesia of this event. We have an anesthetized patient without respiratory depression plus an insensitive pharynx and finally a patient who, on wakening, is alert, cooperative, and not sleepy and groggy for the next 24 hours.

Heptacyclazine may be useful in potentiating the effect of thiopental-nitrous oxide-oxygen anesthesia, similar to the way in which we use meperidine at present. It would produce analgesia without respiratory or cardiovascular depression. Its place in the treatment of pure pain is being evaluated. Here it may fail because of its lack of sedative effect.

At present, the only complication with these drugs is their irritation properties which necessitates an intravenous be running for their administration. The 5-7 minutes which are needed before the patient is unconscious and in a surgical plane of anesthesia also deters their use in a busy operating schedule.

Another intravenous anesthetic agent which does not appear to cause somnolence after operation is a thio-barbiturate called Baytenal.[9] It is sodium 5,5-allyl-(2-methyl-propyl)-thiobarbiturate. The drug is stable in solution for about 36 hours. It is a white powder readily soluble in water and used in 10 per cent solution. Baytenal acts rapidly and produces little respiratory or circulatory depression in therapeutic doses. Four hundred milligrams produces unconsciousness with recovery in 5 minutes and ability to be ambulatory in 10 minutes with no demonstrable after effect. Because of its rapid elimination or detoxification (and no storage in fat) it may prove useful as a constant intravenous drip for longer surgical procedures, similar to the way we now use succinylcholine or thiopental.

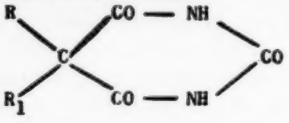
My experiences with the newer thiobarbiturates have not been too satisfactory. Many have worked well on animals but in humans we have seen several side effects, namely venous thrombosis, thrombophlebitis, coughing, sneezing, hiccups and vomiting. This was true also during the early synthesis of thiopental and thioallyl. It may be due to impurities or contaminants and some of these newer drugs may come into clinical use.

Recent work has also been done with intravenous analeptics which seem specific for barbiturates. N-allyl-normorphine (Nalline) is not effective in the treatment of barbiturate overdose. It is effective in treating all opiate derivitive intoxication. Recently, Boyd, from the Pharmacology Department in Kingston, again showed both its ineffectiveness and possible harmful effects in the treatment of barbiturate overdose.

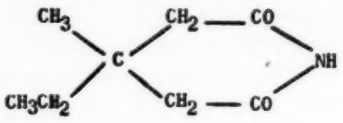
Reports from the Australian[10] as well as the British literature[11] have revealed some interesting studies with two drugs, one of which seems specific for barbiturate intoxication, the other being a respiratory stimulant against any type of respiratory depression. These two new substances, bb-methylethyl-glutarimide (NP13) and 2:4—Diamino-5-phenylthiazole hydrochloride (D.A.P.T.) used in conjunction with the resuscitative regime advocated by Nilsson[12] may further reduce the death rate in barbiturate intoxication.

The chemical structure of NP13 indicates a definite resemblance to the barbiturate ring as seen in Figure 3. In therapeutic doses this drug appears to exert a direct antagonism to the barbiturate. If this drug is given intravenously in high dosage

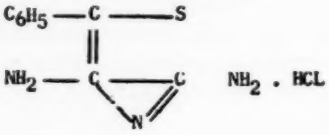
and rapidly it will cause convulsions. Much of this drug is excreted in the urine unchanged. I know of no reports as to what effect it has on barbiturate blood levels or brain barbiturate content.



A 5: di-substituted barbiturate



BB-methylethylglutarimide (NP13)



2: 4-Diamino-5-phenylthiazole hydrochloride
(D.A.P.T.)

Figure 3

Chemical structure of bb—Methylethyl-glutarimide (NP13) and of 2:4—diamino -5- phenylthiazole hydrochloride. (D.A.P.T.) antagonists of and similar in structure to barbiturate.

These same investigators have studied a large number of drugs reported to have analeptic properties against opiates. All of these drugs have either a muscarine like action or are anti-choline esterase drugs and a common chemical linkage is the phenyl-thiazole radical. Testing drugs with this linkage it was found that 2:4-Diamino-5 phenyl-thiozole hydrochloride (D.A.P.T.) was active in the stimulation of respiration in both opiate and barbiturate medicated animals with respiratory depression.

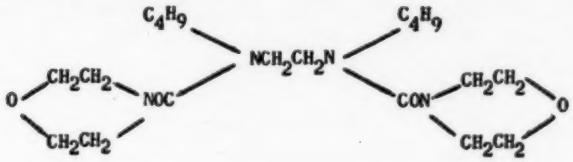
Using a combination of these two drugs intravenously the Australian investigators report success in bringing deeply comatose, areflexic barbiturate intoxicated patients to what they call a "safe state" in a matter of two hours. They then remove the endotracheal tube and treat them as though the patient were recovering from light anesthesia. These investigators feel this has the advantage of obviating prolonged endotracheal intubation or tracheotomy, minimizing possible complications of prolonged coma and is economical in preventing prolonged strict nursing care.

Time alone will tell whether this will be an advance in therapy since now on a careful medical regime alone the mortality rate in barbiturate poisoning is about 1.6—4 per cent.

Still another antidote is an analeptic drug which is said to have marked stimulant effects on both respiration and circulation with an improved margin of safety over the commonly used analeptics. Metrazol, nikethamide and picrotoxin tend to produce convulsions, this tendency being counteracted, if the analeptic dosage is not too large, by the anti-convulsant effect of the barbiturates. They are not as effective in narcotic poisoning.

Figure 4 shows the structure of this new analeptic. Structurally it does not resemble the other analeptics. NN-Dibutylethylene diamine NN dicarboxy bismorpholide is effective in counter-acting the respiratory and circulatory depression caused by both barbiturates and opiates. It has the advantage of not producing convulsions except in excessively large doses. This drug given intravenously, in therapeutic dosage,

is said to also stimulate respiration in the normal unpremedicated subject. It does not have any "amphetamine-like" stimulant action on the central nervous system and does not produce insomnia.



N N' Di butylethylene diemine N N' dicarboxy bismorpholide

Figure 4

Chemical structure of a new antidote for barbiturates.

In subjects depressed with overdosage of either narcotic or barbiturate it will stimulate respiration and raise the blood pressure. The recommended dose is 15 mgm. intravenously. Onset of action is brief, the peak activity is reached in 5-8 minutes and lasts for about 1 hour. How successful this drug will be must await further clinical trials.

Antidotes are also being used with the muscle relaxants. With muscle relaxants most of the anesthetist's attention is focused on respiration and how it is altered, but another important and adverse effect these drugs have must not be overlooked. As well as blocking activity at the neuromyal junction, and producing muscle relaxation with inadequate respiratory exchange, they have inherent in them the ability to block sympathetic ganglia with resultant deleterious effects on the circulation. Occasional patients develop unexplained hypotension of a severe degree. Some have profound circulatory collapse with doses of curare that do not necessarily paralyze the respiratory muscles. Curare may on occasions also have a central nervous system depressant action. While not producing unconsciousness it may block the passage of impulses from centers important in maintenance of both respiration and circulation.

Because of the antidotes, todays anesthetist is probably more liberal with his doses of relaxants. But in some instances the antidote fails to outlast the relaxant or at times the anesthetist is surprised to see adverse effects in the patient following injections of neostigmine, atropine, or nikethamide. The anesthetist is at a loss to explain why the patient suddenly developes an asthmatic attack, a marked tachycardia, an elevated temperature, has a convulsive seizure of just simple atelectasis. Intravenous agents affect people in various ways and should not be used empirically. The antidote may be producing all of these complications.

As regards curare antidotes one which may be used to counteract the apnea occasionally seen after succinylcholine should be mentioned. Of the two enzymes in blood (true cholinesterase in the red cells and pseudocholinesterase in the plasma) the pseudocholinesterase is reportedly responsible for the hydrolysis of succinylcholine. It has been suggested that unduly prolonged succinylcholine apnea be treated with transfusion of whole blood. Fresh blood is preferable, but even after storage whole blood contains some 30 units of pseudocholinesterase per ml. of plasma. There is now a commercial preparation available for clinical trial which is an ethanol fraction of concentrated human plasma and is a subfraction of Cohn's globulin fraction IV-6.

This is said to be a specific antidote for succinylcholine apnea. There are, however, cases reported who have had prolonged apnea from succinylcholine whose serum, when tested, revealed normal enzyme levels. These people were suffering from cancer and inanition. They had altered electrolyte values in the serum, primarily low potassium. It may be that in patients like these, muscle paralysis is difficult to reverse because of a loss of excitability. Antidotes are of no use.

In concluding I want to repeat the statement made by a leading pharmacologist and physiologist with whom I was associated 20 years ago. He still makes it to his students today. "Inhalation anesthesia is the safest anesthetic method, since the patient's own vital processes keep him alive; intravenous anesthesia depends on the patient's ability to detoxify or excrete the anesthetic agent and this may be quite variable, and once the agent is injected you can't get it back". We are developing antagonists and antidotes, it's true, but an anesthetic administration has always been a dangerous experience for the recipient, and the over-all picture would appear that it has become, with the spread of the newer methods, a more dangerous experience. I'm reminded of the modern Dante's (Geoffrey Kay's) poem in which he is describing the type of pit into which the unwary anesthetists may be drawn through putting their trust in false gods, be they new intravenous anesthetic agents, antidotes, or indicator soda lime.

Here rests beneath this grassy plot,
My patient, Mrs. Geer,
Who, being curarized, could not
Exhibit hyperpnoea.
If we could meet a second time,
Less confident I'd be
In "indicator" soda lime:
I'd measure her B.P.!

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INDUCED HYPOTENSION

JOHN W. DITZLER, M.D.*

For many years surgeons have recognized the value of a low blood pressure in reducing or controlling bleeding. In 1945 Gardner[1] employed arteriotomy during neurosurgical procedures. The problem of purposefully lowering blood pressure has been re-explored and the field of deliberate hypotension has come to the fore in the last few years. Enthusiasm exhibited by some investigators would propose it as a panacea for surgical bleeding. Our medical colleagues have long insisted that the patient undergoing anesthesia and surgery have not only a plentiful supply of oxygen but that the blood pressure not be allowed to fall. There has been perplexity on the part of the anesthetist who in one room worries because a patient's blood pressure has fallen to 90mm. Hg. systolic, while in another operating room, where induced hypotension is to be employed, the anesthetist is unhappy because the patient's pressure refuses to go below 90. This paper will indicate a basis for the rational approach to the problem of deliberate hypotension.

Purpose of Induced Hypotension

Surgery today is often more extensive than 20 years ago. Radical operations for the cure of malignant diseases and for the correction of congenital and acquired anomalies have been made possible to some extent by new techniques in anesthesia, in better pre-and post-operative care and by the use of antibiotics. Controlled, induced or delibrate hypotension has been advocated during some of these procedures to conserve blood loss, reduce the number of whole blood transfusions, facilitate surgical dissection and hence achieve a reduction in the operative time as well as to obviate some of the difficulties encountered in large tissue dissections. Dripps[2] has stated, "The incidence of post-transfusion viral hepatitis continues to be a hazard. Sensitization of a recipient to subsequent transfusions has always posed a problem. With the discovery of numerous Rh groups an important source of sensitization was uncovered. Other similar, but as yet incompletely studied factors, remained to be evaluated. The cost of transfusions to the patient, the availability of whole blood, and the proper temperature for storing blood are problems requiring solution. The occurrence of generalized unmanageable bleeding from traumatized surfaces during operation appears related to multiple transfusions in certain instances. Blood stored for more than a few days suffers almost a total loss of platelets, a reduction in the amount of accelerator globulin, one of the substances which acts as a catalyst in the formation of thrombin from prothrombin, and an increase in potassium. Furthermore, with passage of time increasing fragility of stored cells occurs so that approximately 30% of the infused red cells may be destroyed within 24 hours if a transfusion consists of blood more than 14 days old. For these various reasons one would like to decrease the number of transfusions".

Does induced hypotension really significantly reduce the blood loss and decrease the operative time? Various authors[3,4] have stated that blood loss is only 30 to 50% of that seen with normotensive techniques. Other studies[5,6] have indicated that operations are completed in far less time and that the patient seemed far less prostrate post-

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operatively following deliberate hypotensive techniques compared with normotensive techniques. Ditzler and Eckenhoff[7] have reported a study of 90 patients undergoing surgical procedures in whom the blood pressure had been deliberately lowered and compared the results with 84 patients having similar operations without induced hypotension. Patients were matched as to the type of operation and skills of the surgeons. A reduction of blood loss in terms of percentage was found to be of little value unless compared with the actual amount of blood saved and the amount of blood still necessary to be transfused. In a series of radical dissections of neck and pelvis the reduction in blood loss was approximately 35%. This represented one unit of blood saved in dissections of the neck but 2 units saved in resections in the pelvis. It still remained necessary to use 2 units of blood in the instance of the radical neck dissection and 4 units of blood in the case of radical dissections of the pelvis. These authors indicate deliberate hypotension does not guarantee a reduction in blood loss. There were instances when the blood loss was considerably in excess of the average seen during deliberate hypotension. Some surgeons commented that occasionally patients demonstrated more oozing at lower blood pressures than at higher pressures. It is of interest that the operative time in this study was not usually reduced by the use of hypotension and in some instances was considerably longer during periods of hypotension. One might argue that the drier field permitted a more extensive and complete dissection, and allowed for better teaching of residents. It also reduced the pressure on the surgeon for speed. The study also indicated that surgeons by experience alone could considerably lessen blood loss and operative time.

Circulatory Physiology—General Considerations

Tissue oxygenation involves multiple factors of which the important circulatory factors are 1) an effective blood volume containing an adequate amount of hemoglobin, 2) the peripheral resistance as a whole as well as in selected areas of the body and, 3) the cardiac output. In general, flow is equal to pressure divided by resistance ($F=P/R$). If for example, mean blood pressure is 100 mm. Hg. and resistance is arbitrarily measured in units of ten then the flow would be: 100/10 or 10. If the blood pressure is allowed to fall to a mean of 80 mm. by virtue of peripheral vasodilitation, total peripheral resistance is less (arbitrarily 8 units) and accordingly the flow would be 80/8 or again 10. If, however, the pressure is reduced from 100 to 80 mm. Hg. by means of hemorrhage, and compensatory vasoconstriction occurs increasing peripheral resistance (arbitrarily to 12 units) then the flow is 80/12 or 8.3. Hence the flow of oxygenated blood to the tissues during hemorrhage is reduced.

In 1918 Sir Henry Dale shed light on the problem of circulatory physiology when he demonstrated the differences between hypotension induced by intravenous histamine and that seen following intravenous acetylcholine. In both instances the blood pressure was decreased to approximately the same level. With histamine there was arteriolar constriction and increased capillary permeability, loss of plasma from the capillary bed, and the return to a normal blood pressure did not often occur. This is the picture that is commonly seen with reactions of the body to hemorrhage or traumatic shock. On the other hand the picture with acetylcholine was one of arteriolar dilatation, no loss of plasma from the capillaries and a rapid return of the blood pressure to normal levels and this is what is achieved with hypotensive techniques employed today.

Blood volume in order to be an effective volume must be as near normal as

possible when the peripheral resistance is altered. The cardiac output must not be in doubt by reason of myocardial disease and the blood which is circulating must carry a maximal amount of oxygen. Ignorance of these considerations early led to increased morbidity and mortality with induced hypotension.

Circulatory Physiology of the Patient Undergoing Induced Hypotension

Dripps [2] stated that the factors which determine whether the body can tolerate hypotension appeared to hinge upon the following, "a) the duration of hypotension b) the degree of the hypotension c) the previous condition of the blood vessels . . . if these vessels are sclerotic or otherwise abnormal, changes in their caliber in response to hypotension may not occur as readily as with normal vessels and an insufficiency of blood flow may result d) the metabolic needs of the tissues during hypotension, again with particular emphasis on the heart and brain; the lower the metabolic requirements the greater is the reduction in the supply of blood which can be tolerated . . . Likewise, the heart may be better protected than one might imagine because it is being called upon to do less work, if there be lessened peripheral arterial resistance. The coronary arterial blood supply may be curtailed but so may the demand for this blood. e) the liberation of specific depressor substances from ischemic tissues."

A study of the physiological alterations associated with hexamethonium induced hypotension was made by Van Bergen[8] in 1954. Studies were carried out on 14 patients either before or during surgical intervention. The patients were anesthetized by a standard technique and hypotension was obtained with hexamethonium drugs. Intra-arterial blood pressure recordings were done and catheters were inserted into the external jugular vein and the right atrium for venous pressure studies. Circulation time was determined by injecting methylene blue. By the Van Slyke method arteriovenous oxygen difference of the brain was determined. A "Coleman anoxia photometer" was used to study relative arterial oxygen saturations. Electrocardiographs were also taken. Their conclusions are as follows:

Circulation times, oximeter studies and EKG as well as the electroencephalograms indicate that the circulation within vital organs may be reduced to such an extent that severe hypoxia can result. This was particularly true of the elevated portions of the body. Postural drainage in combination with hypotension, as is employed occasionally to further decrease the blood pressure, was found to be more deleterious when the patient was in Fowler's position. The impression obtained from Van Bergen's studies is that serious hypoxia can occur to the heart and to the brain during deliberate hypotension if those areas of the body are placed in such a position that venous return to the heart is deficient and gravity offsets any normal tendency for the increased blood flow seen by reason of vasodilitation. Hence the dangers of hypotension which are always potential are certainly magnified if the patient is in the head-up position.

Stone and Mackrell[9] have studied the effect of deliberate hypotension on cerebral blood flow. Hypotension was induced with hexamethonium, histamine, and protoveratrine. They found that a fall of 44% of the arterial blood pressure with a concominant 46% reduction in cerebral vascular resistance failed to produce significant changes in cerebral blood flow or metabolism. Cerebral blood flow was maintained despite falls in the arterial blood pressure because of the decrease in cerebral vascular resistance. Their conclusions indicate that adjustment was not good in the aged patient

because of sclerotic vessels which can not adjust to a decrease in cerebral vascular resistance. The oxygen consumption was *not* changed. Palmore[10] indicates that the slow awakening of patients undergoing deliberate hypotension is due to a lower basal metabolic rate and to slower elimination of drugs rather than one of brain hypoxia.

Renal function is nearly always decreased during anesthesia and surgery. During periods of hexamethonium hypotension however the fall in blood pressure does not cause a decrease in renal blood flow, according to De Wardener.[11] More studies on this aspect are needed. The two organs which seem to be most seriously affected by the least amount of deviation from normal would appear to be the heart and the liver.

Methods of Induced Hypotension

I. Arteriotomy

The use of arteriotomy was abandoned by most investigators because hypotension thus produced was like that of hemorrhagic shock. Hale[12] states "It may seem and it may be true that hypotension with vasodilatation is safer than hypotension with vasoconstriction. Every animal organism which suffers hemorrhage, however, responds by preserving as well as possible the blood supply to the vital areas while temporarily denying it to other regions. If in hypotension by vasodilatation all tissues are supplied equally without regard for the greater needs of some, this method may not be safer than hypotension with vasoconstriction." The bulk of published data would indicate that the safety of deliberate hypotension in surgery depends on HOW the pressure is lowered rather than the actual levels obtained. Most investigators feel that the method of arteriotomy can cause over-constriction leading to tissue hypoxia. It is also felt to deprive the patient of hemoglobin thus hindering oxygen transport.

II. Mechanical means

Positioning the patient with the operative site uppermost while under normotensive anesthesia may occasionally decrease wound bleeding but results are unpredictable, and at times dangerous. Special chambers have been devised in which the legs may be encased and kept in a dependent position. Suction is applied to these chambers in order to pool blood in the legs. These methods alone are not used extensively but are adjuncts to other methods.

III. Spinal Sympathetic Blockade

In this technique the usual vasopressor support of blood pressure is omitted, the legs are placed in a dependent position and general anesthesia is usually added. The peripheral arterioles are thus dilated by a preganglionic sympathetic block. This method is often very effective and can be fairly well controlled by use of catheter spinal techniques using short acting procaine and vasopressors for termination of the period of hypotension. It is probably the preferred technique for procedures below the diaphragm since it not only lowers blood pressure but likewise produces analgesia and muscular relaxation. Light general anesthesia is added for patient comfort and to insure an adequate respiratory exchange.

IV. Ganglionic Blocking Agents

Those drugs chosen are usually paralysants to autonomic ganglia without any specificity. Predominantly they produce arteriolar dilatation and consequent lowering of peripheral resistance. Such drugs have effects other than lowering of blood pressure; such as cycloplegia and a minimal curariform activity. These drugs should not be

preferentially employed where profound relaxation is required, such as in major abdominal procedures because these drugs used with deep general anesthesia or added curare for relaxation may be additive. Patients may not breathe for hours postoperatively or have prolonged vasomotor depression. Most frequently used are hexamethonium compounds and Arfonad,® (trade name) a thiophanium compound. Hexamethonium drugs are administered by intermittent injection but the results are often unpredictable as to effect and duration. Arfonad is the preferred drug since its effects are transient enough to require a titrated intravenous drip. Young people are more resistant to these drugs than the older age groups. Some patients get no response until large quantities have been given and then remain severely hypotensive for long periods. In other patients an initial satisfactory response is obtained but they then become refractory to subsequent doses. With Arfonad it is probably wise not to exceed one gram total dose irrespective of the procedures duration. If a satisfactory fall in blood pressure is not obtained with 75 to 100 mgm. in 10 to 15 minutes the use of this drug as well as the hypotensive technique in the patient should be abandoned.

With all hypotensive techniques young people are often more refractory, with falls in blood pressure more difficult to obtain. Less anesthesia is required during the hypotensive period and awakening time may be delayed. Cycloplegia often persists 24 hours when ganglioplegics are used. Reactionary hemorrhage must be prevented by raising the blood pressure toward normal before body cavities are closed. Two points of paramount importance are: (a) Normal blood volume preoperatively, and replacement of blood loss the instant it occurs during surgery. Hence sponges must be weighed. (b) Maintenance of maximal respiratory exchange. This requires continuous use of oxygen and frequently assisted or controlled respiration. The blood pressure is lowered to that point where bleeding is considerably lessened. Often this can be achieved at 80 mm. Hg. but on occasions it has been carried as low as 50 mgm. Hg. Theoretically anything above capillary perfusion pressure (32 - 40 mm. Hg.) would be adequate but this risk is not justified; hence pressures are usually sought in the 70 - 80 mgm. range.

Hazards of Deliberate Hypotension in Surgery and Contraindications

Hampton and Little[13] reporting the results of a questionaire sent to various anesthetists in Great Britain and the U. S. in 1953 indicated that 322 physicians employed the technique of controlled hypotension in a total of 27,930 cases. Complications were noted to be higher when the blood pressure was reduced below 80 mm. The overall incidence of complications was 1 in every 31 cases. Supression of kidney function in the form of anuria or oliguria occurred 106 times. Thrombosis of the various essential arterial vessels such as the cerebral vessels, retinal vessels and coronary arteries were reported in 50 cases. Cardiac arrest or cardiovascular collapse in general occurred in 58 cases, and was frequently followed by death. The most frequent complication which occurred was that of reactionary hemorrhage, occurring 243 times. There were 96 deaths or 1 in 291 cases. Since this early report it has been the impression of careful investigators that the mortality for comparable surgery is no greater than with normotensive techniques of anesthesia and surgery with massive transfusions. In this country little has been said of reactionary hemorrhage since the technique here is to insure a normal pressure prior to wound closure. The author's own experience would agree that morbidity and mortality are no higher with induced hypotension where care in the selectivity of patients is exercised. Unfortunately the elderly hypertensive cardiac

patient who should be spared massive transfusions and prolonged surgery should be denied this technique. Likewise it should not be used on those with moderately advanced arteriosclerosis, hepatic, renal, or cerebral disorders.

Indications for Induced Hypotension in Surgery

(a) Major surgery on large blood vessels and cardiac operations: In these cases hypotension can be achieved by deliberate hypothermia which in addition to lowering body temperature and oxygen utilization also lowers the blood pressure. (b) Certain neurosurgical procedures, i. e. the ligation of intracranial aneurysms. Here hypotension should be produced only at the time the surgeon has the greatest need for it. (c) Extensive surgical dissections where many planes of tissue are to be dissected and the predicted blood loss will be in excess of 2000 cc. Here the sparing in transfusions to the patient is of considerable importance as well as providing greater facility for surgical dissection.

In general, induced hypotension should be used on carefully selected patients where the risks without hypotensive techniques exceeds those of normotensive procedures with massive transfusions.

SUMMARY

Induced hypotension in surgery is accomplished by deliberately lowering the blood pressure to 70 or 80 mm. Hg. systolic by means of ganglioplegics or spinal anesthesia wherein the peripheral arterioles are dilatated and capillary permeability remains unchanged. If the patient has and is maintained with an adequate blood volume, is adequately ventilated with oxygen enriched atmospheres, and is kept in a level or Trendelenburg position, the safety to the patient is no less than comparable procedures done with massive transfusions. Blood loss is decreased but the reduction is such as to question its use in other than selected cases. Complications which follow the use of deliberate hypotension are more frequently associated with blood pressures that are kept below 70 mm. Hg. systolic and occur in those patients in whom selectivity has not been exercised.

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PREPARATION OF NATURAL FOODS FOR TUBE FEEDING

JAMES BARRON, M.D.*

Natural whole foods have been extensively used for tube feeding at the Henry Ford Hospital since 1951. (1) Natural foods provide excellent sources of protein, fats, carbohydrates, vitamins, minerals plus all other discovered and yet to be discovered essential nutrients. A few decades ago, the list of essential nutrients was quite simple, and now the list is quite long and undoubtedly will grow longer in the future. The complexity of nutritional needs increases with the passage of time.

Natural whole foods are quite inexpensive when their cost is compared with any manufactured feeding formula (either oral or intravenous). In addition to being low in relative cost, their tolerance by the body is easily predicted because the body has been accustomed to their use over long periods of time.

For the most part, small polythene tubes of less than 2.5 mm. have been used for tube feeding. Obviously some form of liquefication is necessary for natural foods to be passed through these small tubes except in the case of milk and fruit juices. For supplying adequate pressure and a constant rate we routinely use a food pump. These preparations are best tolerated when given at slow constant speeds. This is an absolute necessity for all seriously ill patients and in every duodenal or upper jejunal feeding. A list of a few common foods with their protein and caloric content will readily show that natural whole foods contain ample sources of protein and calories:

	Amount	*Protein*	*Calories*
Milk	1 qt.	35 gms.	700
Powdered Fat Free Milk	17 oz.	178 gms.	1780
Banana	One	1 gm.	88
Egg, Whole	One	6 gms.	75
Rice, Cooked	½ cup	3 gms.	119
Tomato Juice	¾ cup	1.8 gms.	42
Sugar	1 tbsp.	———	58
Medium Fat Beef, Ham	2 oz.	14 gms.	145
Ice Cream	⅓ cup	3 gms.	145
Peas	⅔ cup	5 gms.	91
Potato Baked	1 med.	2 gms.	98

Three methods for preparing these natural foods for tube feeding will be presented: Strained baby foods, blenders and serum mills. (2) (3)

Strained Baby Foods: Many varieties of strained baby foods may be purchased at almost any grocery store. These have already been liquefied and strained. They may be readily mixed with milk, eggs, fruit juice, etc. A brief list showing samples of some of the strained foods available follows:

	Protein	*Fat*	*Carbohydrate*	*Calories*
Beef, Strained—one can or jar	14.6 gms.	4.9 gms.	———	103
Chicken Strained	13.9 gms.	9.2 gms.	———	138
Liver & Bacon, Strained	14.8 gms.	7.2 gms.	———	124
Veal, Strained	15.0 gms.	5.0 gms.	———	105
Peas, Strained	5.2 gms.	.62 gms.	10.7 gms.	67
Beets, Strained	1.5 gms.	.15 gms.	10.7 gms.	51
Garden Vegetables, Strained	3 gms.	.7 gms.	8.0 gms.	50

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A sample feeding preparation using milk, eggs, strained meat and vegetables is as follows: (Fig. 1)

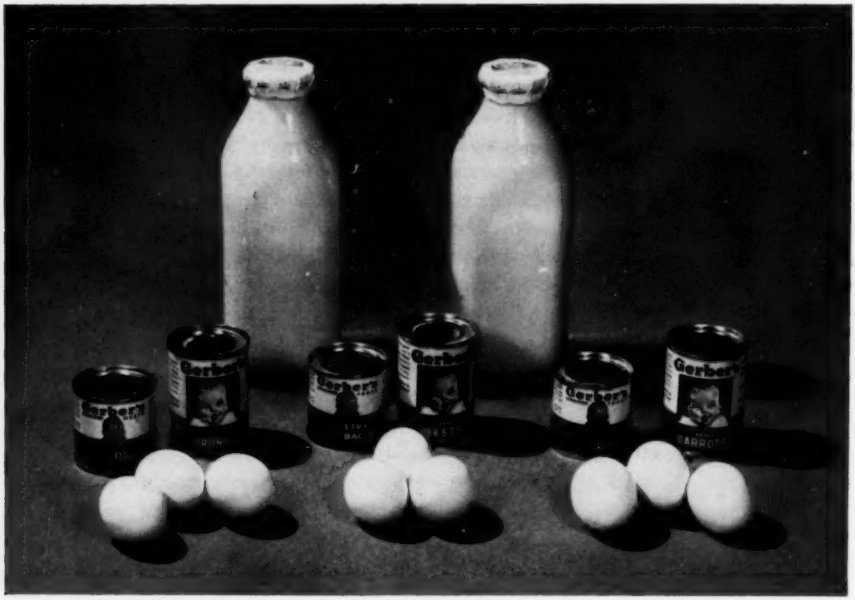

Figure 1

	Protein	*Calories*	*Retail Cost*
3½ oz. Strained Meat (Beef)	14.6 gms.	103	.23
4½ oz. Strained Vegetable (Beets)	1.5 gms.	51	.11
3 eggs	18 gms.	225	.12
Milk ⅔ qt. (Homogenized)	23.3 gms.	466	.14
	57.4 gms.	845	.60

This is only a sample and the various constituents may be changed as desired. Taste plays no part in selecting the food. However, the patient is more comfortable if we keep the composition reasonably near that of a normal diet. This is easily mixed with a large spoon, eggbeater or blender. Straining through a fine mesh wire gauze strainer is advisable. This is readily prepared for home use.

Mechanical Blenders and Juice Extractors: Mechanical blenders are satisfactory for small scale use. (Fig. 2) The mechanical extractors are satisfactory for extracting the juices from fresh fruits and vegetables. In using a blender, one must be careful to observe the following:

1. Remove bones and seed.
2. Do not overload machine.
3. Add adequate liquid to give an active vortex when running at full speed.
4. Homogenized milk should be used if milk is to be added. Regular milk will form butter.

5. Each jar load must be allowed to run for at least 4 or 5 minutes.
6. All liquefied food must be carefully strained through a fine mesh wire gauze strainer. This is most important and it must be repeated at least several times. This is necessary to remove the fibrous material and prevent plugging of the tube. One or two eggs may be added to replace the protein lost by straining.

Figure 2

This straining is facilitated through stirring with a large spoon by gently scraping the concave bottom of the fine mesh strainer with the convex edge of the spoon. Mechanical juice extractors are available in many sizes and are quite useful for extracting juices from fresh fruit and vegetables.

Serum (*Colloid Mills*): (Fig. 3). For large scale use, these large machines are essential. The machine has a water jacket for cooling purposes. The particle size can be regulated by means of a micrometer adjustment. They are easily sterilized by using steam piped into the machine. We have used these extensively at the Henry Ford Hospital since 1952.

COMPARATIVE COST

	Amount	*Protein Cost*	*Calories*	*Retail Cost*
Regular Food	Varied as desired		——— cheapest of all	
Milk	1 qt.	35	700	.22
Powdered Milk (fat free)	17 oz.	204	2800	.39
Strained Baby Food (meat, vegetable, eggs, milk)	3 liters	173	2535	$ 1.80
Manufactured Dry Milk Feeding Formula	1 lb.	105	1760	$ 1.64
5% Glucose Saline	1 liter	0	200	$ 2.50
I. V. Protein Hydrolysate	1 liter	50	400	$ 5.00
Manufactured Tube Feeding Protein Hydrolysate		65	900	$ 6.00
Blood Plasma		27.5		$50.00

Figure 3

SUMMARY

Natural whole foods quite adequately supply the complexity of nutritional needs. They are more reasonable in cost than any manufactured tube feeding or intravenous preparation. Excellent tolerance is readily predicted becaues the body has long been accustomed to handling the natural whole foods. The methods of preparing these foods for passage through small plastic tubes have been discussed.

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MYOFASCIAL PAIN SYNDROMES — PART II

Syndromes of the Head, Neck and Shoulder Girdle

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It is the purpose of this article to point out the basic similarities among a group of syndromes having the common factors of myofascial pain or pain referral. In any particular syndrome the myofascial pain may be primary and uncomplicated, may be primary and complicated by secondary manifestations, or may itself be a secondary manifestation of another affection. In each of these symptom complexes the treatment of the myofascial pain component can be an essential part of the total relief afforded the patient; in many instances such treatment can be curative. The general treatment of myofascial pain has been discussed in Part I of this series[13] so that the present discussion will deal mainly with the details and variations of this therapy in the individual syndrome.

It is difficult to classify myofascial pain by any method other than anatomic or eponymic. Any attempt to classify this pain physiologically meets with the problems previously mentioned. The syndromes hence go under such uninspiring, but accurate, names as cervicobrachialgia, scapulocostal syndrome, and scalenus anticus syndrome.

One group of syndromes appears in the medical practice of almost any physician, specialist or general practitioner, with amazing frequency. This group occurs in the form of aching pain in the head, neck, upper back, shoulder or arm. It has the group characteristics of the myofascial pain syndromes. In short, if it appears as pain in the head it may be called cervicocephalalgia; in the neck—trapezius syndrome or cervicalgia; in the back—scapular syndrome, in the arm—cervicobrachialgia or scapulohumeral syndrome; in the rib cage laterally and inferiorly — scapulocostal syndrome. The syndrome can be named by its own anatomic location if non-radiating, or by its direction of radiation if radiating — e.g. cervicobrachialgia.

SPECIFIC SYNDROMES

1. Tension Headache: It is not the purport of this author to imply that tension headaches are primarily caused by myofascial disease. However, the presence of myofascial changes in the presence of tension headache is often observed and is well documented.[1] It has been rather conclusively shown that the presence of pain in the head will produce neckache, and that reciprocally the presence of neck pain will produce headache in some cases. In the patient with tension headache, relief can sometimes be afforded to a remarkable degree by the application of physical measures of treatment to the neck musculature. [2, 3]

Tension headache can be defined as a dull, fairly continuous headache located usually bilaterally in the frontal or temporal regions and often accompanied by pain at the occipitocervical junction. It shares several characteristics with myofascial pain — the aching, dull, continuous character, the exacerbation by increased activity, emotional tension, changes in the weather, long periods of inactivity or long automobile rides involving constant strain.

Examination of the affected parts will turn up little of significance outside the

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muscular system. All other sources of headache have often been eliminated by the time the muscular component is noticed by the physician. In examining the musculature of the posterior neck and upper back there will appear tender areas in the musculature, usually quite deep. The patient will experience a rather sickening, dull pain in the palpated area. In a significant number of patients (unfortunately far from all of the patients) the patient will immediately complain that his headache has started, or has become worse; in this group of patients the trigger point for the headache can be considered definitely located. In most patients such an easily demonstrable trigger mechanism does not exist. The physician must then rely on established trigger areas of reference for headache in order to treat the proper tender areas effectively.

The trigger areas most commonly involved in tension headache, are located in the cervicoccipital attachments of the long back musculature, in the mid cervical paravertebral musculature, in the mid upper trapezius, in the sternomastoid belly, and in the upper origins of the scalenus anticus, in order of approximate frequency of occurrence. [3, 4] Some of these trigger mechanisms have been singly named, such as "sternomastoid syndrome", but the method of pain production is similar in all. The differences exist only in variations of pain reference on the head. As a group these pains can all be called cervicocephalalgia.

The mechanism of "tension headache" is assumed to be cyclical. It includes a tension situation, tightening of neck musculature, spasm of localized areas of neck musculature, increased tension and worry, increased spasm, and so on, until it leads to possible proliferation of fibrous tissue in musculature with formation of the evanescent "fibrositic nodule". This cycle may start at either a psychologic or physiologic point on its circumference, and can be broken up by entering at any point in the cycle. A therapeutic approach directed at several points in the cycle simultaneously can be expected to produce the best results. An accurate appraisal of collective treatment results is difficult in the face of the information that 50 percent of tension headaches can be relieved by placebos.[5]

Most of the tension headaches seen by this author, if accompanied by myofascial changes, are accompanied by chronic myofascitis. The treatment of the myofascial component of the pain is therefore the treatment of chronic myofascitis of the cervical musculature. This is done by a combination of salicylization, (I have not used a large amount of ergot or caffeine compounds, but their efficacy is unquestionable) muscular stretching, local heat, and trigger point injection.

The muscular stretching is done by means of the "Sayre" sling method. Intermittent traction applied once or twice daily for a period of fifteen minutes is apparently as effective as continuous traction. The sitting position is preferred for the administration of traction. A forty-five degree forward angle of stretch is advocated by some authors, but effectiveness seems as good if traction is exerted straight up. Traction is carried out in three approximately equal increments of five minutes each to a daily upper limit of fifteen, twenty or twenty-five pounds. In refractory cases in heavily built persons as much as fifty pounds may be required. It is better to underestimate than overestimate traction requirements because of the extreme soreness of the neck which may result from excessive weights for a given individual. Amounts are raised successively if no response is obtained. Each traction session is preceded by fifteen minutes of infra red heat to the back of the neck. This is given in the prone position,

since some patients faint if heat is applied to the neck in the sitting position.

Most traction therapy can be given as home treatment. One session of traction instruction and demonstration will suffice if given by an experienced physical therapist. The physician can then see the patient at intervals for verbal instruction in traction weight changes at the same time other therapy is administered by him.

Injection is the major adjunct to traction in cervicocephalalgia. It is indeed usually used prior to traction, for the early discovery of the offending area may obviate the use of traction at all. Once the trigger area or areas are located they are subjected to injection at weekly intervals with the mixture of local anesthetic and hydrocortisone derivative of the physician's choice. If a response is going to occur, it will usually occur after one injection, sometimes will take two injections, and will rarely respond if it has not responded to three consecutive injections. The response as a rule is not permanent after initial injections, for symptoms will recur to some extent within two or three days. However, each recurrence will be less severe than its predecessor. Injections should be continued as long as the patient continues to improve, or until he is well. Traction should be added in the event of injection failure or to potentiate injection therapy; traction may be used *de novo* and *solo* if it is more convenient to patient and physician. A review of tension factors in the patient and his environment is of course essential to ultimate success of therapy.

2. Trapezius syndrome, a cervicalgia, or tension neckache: This syndrome is one that should be called "schoolteacher's neck". It occurs often as a tension manifestation, though almost equally often as the result of relatively "minor" trauma to the neck. As such it forms a major cause of pain in the "whiplash injury" of the neck. It may occur as part of the total pain spectrum in more severe lesions, such as cervical disc, cervical cord tumor, or vertebral metastasis. Its pain is characteristically located in the soft tissues at the side of the neck and top of the shoulders, in the neighborhood of its common trigger point. This trigger point is located in the mid-upper trapezius or in the musculature just superior to the medial, upper angle of the scapula. It is best felt by compressing the tissues against the posterior aspect of the first rib and first thoracic transverse process, or by squeezing the soft tissue of the medial shoulder between thumb and forefinger.

Pain may radiate from the trigger area across the point of the shoulder or to the base of the skull; in the latter instance it becomes a cervicocephalalgia and merges with the above classification of tension headache. This myofascial syndrome thus overlaps the syndrome above it. By so doing it may often spread to cause other manifestations of the neighboring syndrome. This type of behavior is common among certain patients (those with the "fibrositic diathesis") so that a patient starting with a whiplash injury may develop first a trapezius syndrome, and later go on to develop the whole gamut of head, neck, shoulder and arm syndromes.

This syndrome seems to have a particular affinity to exacerbation by sudden increases in activity. A tension neckache may be under good control until the patient decides to polish the car, paint the walls, take a long automobile trip, do her own ironing or mark a batch of examination papers. Such activities are those which require prolonged muscular tension in the upper shoulder segments. Avoidance of predictable sources of exacerbation is therefore an integral part of therapy of this syndrome. In cases involving the patient's occupation, such as stenography, this often

presents a sizable problem since the patient cannot stop typing on the job and cannot change jobs because of lack of training. I suspect that heavy brassierre straps are also severe offenders in the production of continuous shoulder tension, but modern engineering knowledge has not yet solved this problem to the satisfaction of the wearers.

In the direct management of this syndrome the combination of trigger point injection and cervical Sayre sling traction is again the foundation of treatment in addition to systemic anodynes. The schedule of traction treatment is the same as that used for the cervicocephalalgias. The relief of tension by interview assistance is again important.

3. Scapulohumeral syndrome; scapulocostal syndrome (the scapular syndromes): These two names are not synonyms. The scapulocostal and scapulohumeral syndromes are two separate entities, but are discussed under one heading here because of the marked similarities in their causes and treatment. Both syndromes have trigger areas in musculature arising or inserting on the scapula, producing distant radiation of pain. Both syndromes have a common occupational stress factor appearing often in the history. Although mental stress remains important in these syndromes as in others discussed[13], there is an important postural and repetitive motion factor here. The entire group of scapulohumeral and scapulocostal manifestations are discussed by Russek in his excellent article[6]; however, he does not differentiate the various components of what he considers a single syndrome. He includes symptoms radiating from the scapulocostal articulation and resulting he feels from abnormalities of this articulation. I prefer to use a strict anatomically descriptive interpretation of terms until more basic evidence is accumulated concerning the true origin of these syndromes. Hence, in this discussion "scapulocostal" means pain referred from the scapula to ribs; "scapulohumeral" means pain referred from the scapula to the arm (and should more accurately be called scapulobrachial).

The scapulohumeral and scapulocostal syndromes appear very commonly in consort. Therefore, the combined finding of scattered scapular area trigger points plus significant arm and costal cage pain is also common.[7] One of the most usual precipitating factors is the ocupational factor mentioned above, and Russek refers to the following categories of worker as particularly prone to the illness—machine operators, pressers, fitters, seamstresses and cutters—to which again can be added schoolteachers and stenographers.

The scapulohumeral and costal complexes can also appear as part of any affection of the glenohumeral joint region, as secondary manifestations of bursitis, rheumatoid arthritis or osteoarthritis, or as the secondary manifestations of "minor" trauma in the shoulder region. Continued, unaccustomed strain, or sudden, violent strain (without muscular or ligamentous rupture) may produce the syndromes, or they may appear as secondary pain factors following destructive injuries such as fractures or ligamentous tears. Root compression syndromes of the cervical spine may set up cervicobrachalgic reference patterns of pain which develop into full blown scapular syndromes by the production of trigger points within the zones of reference. Certain forms of the shoulder-hand syndrome are simply scapulo-humeral syndromes which have been precipitated within the zone of reference of other pains (viz—cardiac pain). In like manner the scapulocostal syndrome can be a secondary development in the reference

area of an intercostal neuritis (for which it is often mistaken), or in the zone of thoracic root compression reference.

In each of the above instances, the scapular syndrome is not primary; however, the treatment of the syndromes will often lead to remarkable relief of what was thought to be the "primary" pain. Indeed the scapular syndromes can be primary in themselves, and their subsequent treatment results in complete relief of symptoms.

In the scapulohumeral syndrome the reference area of pain is in the entire lateral upper arm, forearm, the fingers and the thumb. The trigger points are located in the infraspinatus or at the medial scapular border. A pectoralis major trigger point often accompanies this syndrome, as does a long biceps tendon area, but these cannot be strictly considered part of this syndrome.

In the scapulocostal syndrome the pain is referred laterally and downward to the lateral, anterior, inferior rib cage. A common complaint in women is pain and tenderness just below the breast in the rib cage; pain and tenderness in the mid-axilla and inferior axilla is also common. There is also often a complaint of tenderness at the medial border of the scapula, noticed by the patient when he lies on the affected side, lies on his back, or leans his back against a hard chair. The trigger point for this syndrome is almost invariably located at the medial scapular border, or in an area bounded by the mid-point of the medial scapular border, the inferior tip of the scapula, and by the midline of the back between corresponding levels of vertebrae.

These syndromes may be encountered in any stage of activity—acute, sub-acute or chronic. In the acute stage, intense heat is applied most easily with the steam cabinet (twenty minutes twice daily) or very hot packs (hydrocollator—same time periods); codeine is often required, and hospitalization is not uncommon. If home treatment is imperative, home hot packs may be used, or a heat lamp will do. When the diffuse tenderness and extreme muscular excitability and spasm of the acute stage have subsided, the tenderness will usually localize near the trigger areas. These areas should then be injected at intervals with an anesthetic-hydrocortisone combination. The frequency of injection should be timed to allow significant improvement, or determine the lack of it, before repetition of injection. As the subacute stage passes into the chronic, or convalescent, traction may be added, particularly if there has been involvement of the upper scapular attachments. Salicylization is continued throughout the entire treatment course and the patient is allowed to perform no activities which can be predicted to cause exacerbation of the syndrome. As healing occurs, a compromise must often be made in allowing the patient to return to work. This must be done with the patient's understanding that this will prolong the necessary period of treatment. In the presence of recurrent attacks of these syndromes a job change is sometimes essential; under any circumstances some modification of the precipitating type of work should be attempted. This is easier said than done.

4. Scalenus anticus syndrome: This syndrome, nebulous as it sometimes appears, has become a fairly frequently diagnosable entity. In its classical form it includes cervicobrachalgia, vascular symptoms in the form of decreased pulse or blood pressure, secondary neurologic findings of anesthesia, hypesthesia, paralysis or weakness in the arm, and tenderness over the scalenus anterior. This syndrome is a manifestation of the effects of myofascitis of the scalenus anticus muscle, and the syndrome is hence amenable to those treatment methods effective in myofascitis. Myofascitis of the

scalenus anticus is an extremely common finding among the group of head, neck and shoulder pain syndromes. It is not necessarily accompanied by any secondary findings in the arm, and is probably more commonly seen without such secondary findings or symptoms.[8] During the course of the syndrome, the anterior scalene muscle causes the production of pain successively or together in each of the segments of segmental distribution—sclerotomal, myotomal and dermatomal.

The pathogenesis of the scalenus anticus syndrome can be postulated as follows. During the first stage of the syndrome (usually unrecognized as such), the muscle is moderately in spasm, slightly tender to the touch and sometimes spontaneously painful in situ. In this stage of early involvement a classical trigger-reference combination develops and may produce pain in the anterior chest, anterior or posterior arm, or upper, medial scapular border region. The pain distribution at this stage is sclerotomal[9, 10] (referred to the fascial, osseous, synovial and ligamentous radiations of the segment) and myotomal (directly interpreted pain in the muscles.)

As the pain and "spasm" or increased tension of the muscle increase, the syndrome progresses to its classical form. This can be differentiated into two types—a superior type, involving compression particularly of C-6 and C-7 roots, and an inferior type compressing the C-8 and T-1 roots and the subclavian artery.[11] The pain distribution then corresponds to the dermatome involved in the compression, and the weakness corresponds to the myotome of the compression. In addition to these obvious causes of pain, the additional formation of trigger points within the reference areas may set up new, secondary pain syndromes.

The treatment of the scalenus anticus syndrome is the treatment of the scalenus anticus muscle. Manifestly, refractory cases should be surgically treated; results are reported as satisfactory. However, conservative treatment is quite effective in most cases, and certainly is all that is indicated prior to the development of secondary neurologic signs.

Treatment is predicated not on the stage of development of the syndrome as described above, but rather on the phase of myofascitis in which the scalenus anticus is discovered. Regardless of physical secondary findings, the acutely inflamed scalenus is treated as any other acutely inflamed muscle, the subacute as a subacute muscle and so forth.

During the acute stage, twice daily intense heat on the neck, plus salicylization is used; positioning of the neck, with the ear down toward the shoulder on the affected side, and the neck in flexion may be helpful. During the subacute stage, injection of the scalenus is begun, with the injection aimed at that portion of the body or tendinous origins which seem most involved. As the muscle quiets down it is subjected to stretching by Sayre sling neck traction. It is important not to carry the protective positioning of the neck beyond the acute stage, for this will result in secondary contracture of the scalenus and an increase in secondary signs.

During the chronic or convalescent phase, active exercise may be given to raise the point of the shoulder and thereby prevent stretch of brachial plexus components over the first rib;[12] the efficacy of this maneuver is open to question. Again, occupational adjustment may be important since the scalenes are important positioners

of the head and neck in many occupations. Also emotional tension factors have repeatedly been proven important in this syndrome and should be worked through with the patient.

It should be emphasized that the scalene syndrome often exists without secondary effects on the brachial plexus or axillary artery. Its recognition at the stage of trigger point or local pain reference will materially reduce the chances of development of secondary manifestations.

In a subsequent issue of this journal will be discussed the myofascial pain syndromes of the trunk and pelvic girdle.

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THIRTY YEARS OF CLINICAL PSYCHOLOGY

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During 1956 clinical psychology will be celebrating the sixtieth anniversary of its founding as a separate psychological group. Thus it is young among the professions, but since the first psychological clinic was organized at the University of Pennsylvania by Lightner Witmer in 1896 [1,9] much progress has been made. The scope of clinical psychology has been broadened, and the rapid advances up to 1946 have been reported by Brotemarkle[2] and numerous others in recent books[3,5] and current psychological journals. Both authors of the present paper have been doing work in clinical psychology for more than 30 of these 60 years, one for approximately 30 years, and the other for 13 years at this Hospital. Hence, most of the material for this paper has been drawn from accumulations of data in our psychology section here during the period from early 1926 to 1956.

Historically, the first patient of which there was a record at Witmer's Clinic[1,4,9] was that of a "chronic bad speller" referred by a school teacher asking for help. In addition to various psychological difficulties, this boy was found to have poor vision and other physical troubles for which he was referred to a physician. From this sort of simple beginning, clinical psychology has grown and expanded to include not only the mentally retarded or handicapped individual, but also those of normal or average ability, the superior, the precocious, or any other children, adolescents, or adults who might present educational, vocational or behavior problems or other troublesome deviations calling for psychological adjustment. Thus all kinds of schools, courts, guidance clinics, homes, industries, agencies, and hospitals have become psychological laboratories for men and women working with people in accordance with this new method termed clinical psychology.

Although the term "clinical" was borrowed from medicine, clinical psychology was not meant to be merely medical psychology. In fact, Witmer[9] and his associates pointed out that just as clinical medicine is not what the term literally implies,—namely the work of a practicing physician at the bedside of a patient, so clinical psychology is a method and not a locality. Then, as now, patients were presented to professional groups or to advanced students of medicine or psychology as "clinics" to illustrate symptom syndromes or to help in clarifying diagnostic categories and planning appropriate therapy. Throughout the years clinical psychologists have been interested in observing and studying the individual to determine the cause of his deviations, and *with a basis in the science of normal development,* to work out treatment methods to help adjust the individual within his environment, or when this is not feasible, transferring him to an environment more suited to his needs. Individuals have been examined at intervals to determine their reaction patterns and capacities so that the next steps in their development or in the modification of their behavior could be planned. The main objective of these studies, supplemented in later years by formal psychological tests and inventories, has been to point the way toward the production of preferred patterns of human behavior in certain individuals stressing

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not only corrective, but also preventive, directive, and creative phases as well. The process of psychological evaluation, counseling and therapy applied so as to effect a desired change in the persons studied, has thus become known as the "clinical" method.

Since there were few psychologists in general hospitals when we began our work as the first one here in 1926, one of our duties was to explain to the staff some of the possible areas of usefulness of psychological services. A paper which we presented at that time,[6] besides referring to some of the foregoing background of clinical psychology, listed ten different specific uses which we were beginning to make of psychological evaluations of hospital patients. Other contributions which we have made along this line have appeared by request in connection with various symposia setting forth specific material on the work of a psychologist in a division of neuropsychiatry[7] and in a general hospital[8] working with psychiatrists and other physicians. In each of these articles, and a number of others of a research nature, we have emphasized various phases of general and specific work covering psychological interviewing, counseling or psychotherapy, testing of all kinds, which might include any one of 45 or more different tests, and a group of miscellaneous duties. It was estimated by three psychologists[8] then working full time in our section that time spent in these four areas was distributed approximately as follows: interviewing, 40 per cent; counseling, 30 per cent; testing, 25 per cent; and miscellaneous, 5 per cent.

From a tabulation of 10,000 unselected patients seen for psychological studies, with approximately 333 drawn at random, from each of thirty years, it can be noted in Table 1 that about twice as many children as adults were seen. The male children

Table 1

GENERAL DISTRIBUTION OF 10,000 UNSELECTED PATIENTS SEEN AT THE HENRY FORD HOSPITAL FOR PSYCHOLOGICAL STUDIES OVER A THIRTY YEAR PERIOD FROM 1926 TO 1956.

CHILDREN (UNDER AGE 16)			ADULTS (AGE 16 AND OVER)			
MALE	FEMALE	TOTAL	MALE	FEMALE	TOTAL	GRAND TOTAL
3,742	2,898	6,640	1,603	1,757	3,360	10,000

This table shows that in this large sample about twice as many children as adults were seen, many more of the children were male, and slightly more of the adults were female.

outnumbered the female children about three to two, and the female adults outnumbered the male adults by only a slight margin. Thus it is emphasized that hospital psychologists must be thoroughly familiar with a variety of tests and techniques applicable to children. At the same time they must be familiar with a similar range of tests and techniques applicable to adults because the ratio of patients seen in this large sample during these thirty years was approximately one adult to two children.

At present our list of available psychological tests includes approximately 45 different ones which can be classified in the following major groups:

1. Individual and group intelligence tests, ranging from infant scales through the adolescent and adult levels.
2. Personality tests and inventories for various age levels.
3. Projective techniques for both children and adults.
4. Achievement tests ranging from reading readiness tests through a variety of school subjects of different levels.

5. Performance tests — chiefly form boards and mechanical tests.
6. Special aptitude tests such as clerical and artistic.
7. Occupational and other interest analysis tests.
8. Special tests for measuring mental deterioration.

Any of these tests alone, or in combination with others, may be of assistance in the major problems of diagnosis and planning definitive treatment for patients. Obviously a psychologist cannot be a specialist in all of these areas, but one can acquire much skill in time as the need arises and appropriate divisions of responsibility can be made in accordance with special interests and qualifications of the staff persons available.

Additional study of the records on our first sample of 10,000 patients revealed that not all of them had had sufficient studies to include in a variety of analyses of data. Hence, for other tabulations including types of patients seen, detailed age distributions and others, a total of 6,779 of these records were used. Table 2 gives a summary of these findings. These main groups chosen for use here can be divided into many sub-classifications, but the ten inclusive categories give a wide range picture more suitable for our needs in this paper. All degrees of nervous and mental stability

Table 2

DISTRIBUTION OF MAJOR DIAGNOSTIC GROUPS IN AN UNSELECTED SAMPLE OF 6,779 PATIENTS SEEN FOR PSYCHOLOGICAL EVALUATION IN THE HENRY FORD HOSPITAL FROM 1926 TO 1956

MAJOR DIAGNOSTIC GROUPS	NUMBER	PER CENT
1. NORMALS	1,347	19.8
2. ORGANIC DISEASES AND INJURIES (LARGELY OF THE CENTRAL NERVOUS SYSTEM)	1,280	18.9
3. MENTAL RETARDATION (IQ 70 TO 89) WITH ASSOCIATED PROBLEMS	1,218	18.0
4. BORDERLINE CONDITIONS (MINOR BEHAVIOR DEVIATIONS, HABIT DISORDERS, ETC.)	1,172	17.3
5. MENTAL DEFICIENCIES (IQ BELOW 70)	743	11.0
6. PSYCHONEUROSES	443	6.5
7. PSYCHOPATHIES	178	2.6
8. SPEECH AND READING DEFECTS AND DISABILITIES	173	2.6
9. PSYCHOSES	168	2.5
10. INEBRIETIES (ALCOHOLICS AND DRUG ADDICTS)	57	0.8
TOTAL	6,779	100%

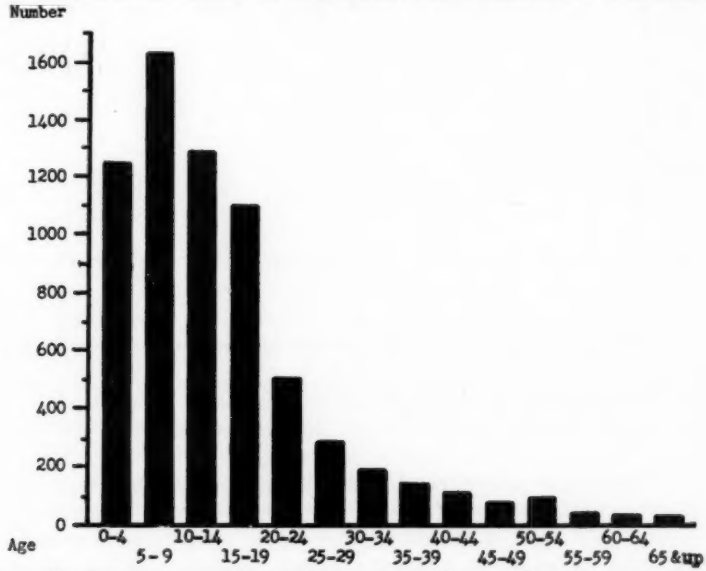
This table shows that most of the major psychological and psychiatric diagnostic catagories were well represented. The largest group of patients seen for psychological study was under the heading of normals, with organic diseases and injuries and mental retardation with associated problems being a close second and third.

and instability are represented. The largest group of the ten categories listed is composed of persons who were regarded as essentially normal individuals with minor psychological problems. Many persons in this group were children being considered for adoption, individuals seeking educational, vocational, and premarital or marital counseling, and others with temporary situational adjustment problems regarding which psychological help was sought.

Chart 1 gives a detailed picture of the age range of our patients. From this it is apparent that the infant and pre-school group was one of the three most important ones in our rather large unselected sample of 6,779 patients. This is because throughout the thirty years we have seen many very young children to help determine suitability for adoption, others for measurement of the type and degree of mental defect or disability so that plans for special training could be made early in life, and still others to determine their readiness to attend an organized pre-school or kindergarten. The largest number of patients was in the age group between five and ten years which is at the early school level. Many of these children presented problems because they had started to school when they were too immature emotionally or intellectually, or both, to make the necessary adjustment. Others because they had some special academic disability such as that shown by their failure to pass reading readiness tests when they were chronologically old enough to start the first grade, or even much older. Two other large groups were at both the beginning and the late adolescent periods. A logical explanation of these findings seems apparent when we think of the many educational and personality adjustment problems likely to arise at these age levels. The total number of patients in the middle age ranges was influenced by the number

Chart 1

AGE RANGE OF AN UNSELECTED SAMPLE OF 6,779 PATIENTS SEEN FOR PSYCHOLOGICAL EVALUATION IN THE HENRY FORD HOSPITAL FROM 1926 TO 1956



From this chart it is apparent that the age range of our patients was very wide and that essentially all age groups were represented. The median age of this entire group of 6,779 patients fell at approximately twelve years, whereas the mode of the distribution was in the group with age range between five years and nine years and eleven months.

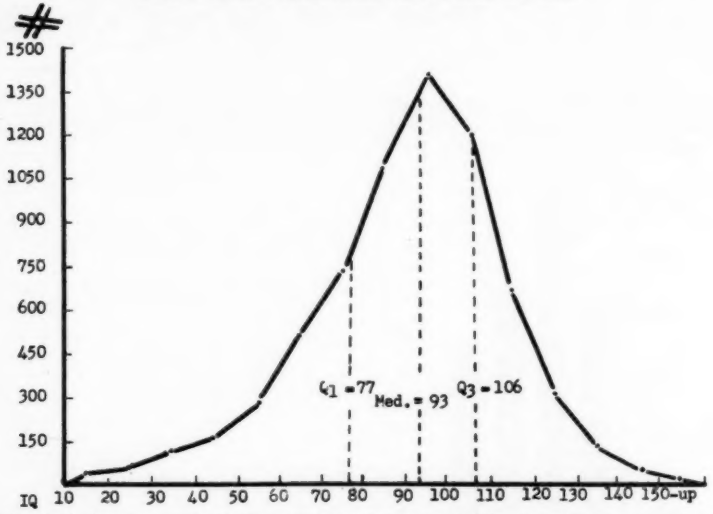
of adult neuropsychiatric patients seen, as well as the frequency with which patients of these ages were seen for other divisions of the hospital. Others, of course, as in the case of many of the children, came directly to the Psychology Section for specific

studies. The rapid decline in the number of patients seen for psychological study after age 50 to 55 is to some extent proportional to the number of such persons seen in the hospital.

Chart 2 shows the IQ distribution of the group of 6,779 patients. The central tendency of the distribution was within the lower part of the average or normal group. The fact that the lower end of the distribution was somewhat more heavily loaded than the higher end suggests that more sub-normals were referred for psychological studies because their problems were more obvious and perhaps more numerous. If we include the lower part of the average group down to 90 IQ, considerably more than half of our patients seen for study were classifiable as at least low average, or better, in general intelligence. However, more than seventeen percent of the total

Chart 2

DISTRIBUTION OF IQ'S AT TIME OF FIRST TEST ON AN UNSELECTED SAMPLE OF 6,779 PATIENTS SEEN FOR PSYCHOLOGICAL EVALUATION IN THE HENRY FORD HOSPITAL FROM 1926 TO 1956



This chart shows a moderately normal distribution of IQ's in this large sample of 6,779 patients although the curve is skewed slightly toward the lower end of the scale. The standard deviation of the total distribution was found to be 23, with the median and quartiles as indicated on the chart.

group were classified as feebleminded (IQ below 70) if we use only their ratings on the first test as the criterion. This is more than five times the expected number in a large random sample of the general population. At the upper end of the distribution we had approximately two and one half per cent of the total group with IQ ratings of 130 and above. This is closer to the frequency with which individuals of the higher IQ levels are found in the general population, but is a larger percentage than expected on a purely statistical basis. The mode of the distribution falls in the 90 to 99 IQ group, which is generally spoken of as the lower half of the average range. The next highest frequency was in the group just above this, IQ 100 to 109 inclusive, covering the upper half of the average range. All other levels of intelligence,

from the most defective to the exceptionally superior, were represented, the lowest IQ's being between 10 and 20 and the highest above 150. If we consider this material along with the range of diagnoses shown in Table 2, and age range shown in Chart 1, it is emphasized that persons of all ages and all degrees of intelligence and nervous and mental stability were seen in this hospital clinic for psychological help with their problems.

Table 3 shows the frequency with which other divisions of the hospital, exclusive of the Neuropsychiatric Division, requested psychological services for their patients. This material is based on a total of 3,597 consultation requests for such

Table 3

IN-PATIENTS SEEN FOR PSYCHOLOGICAL STUDY AT THE HENRY FORD HOSPITAL ON THE BASIS OF 3,597 UNSELECTED CONSULTATION REQUESTS FROM DIVISIONS OTHER THAN NEUROPSYCHIATRY DURING A THIRTY YEAR PERIOD FROM 1926 TO 1956

DIVISION	NUMBER OF REQUESTS	PER CENT OF TOTAL
Pediatrics	2,085	57.9
General Medicine	797	22.2
Dermatology	193	5.4
Gastro-Intestinal	113	3.1
Metabolism	98	2.7
Cardio-Respiratory	65	1.8
Neurosurgery	78	2.2
All Other Surgical	168	4.7
Total	3,597	100%

This table shows that, exclusive of Neuropsychiatry where for many years most of the patients were seen routinely for psychological study, the greatest number of consultation requests came from the Department of Pediatrics.

service taken at random over the thirty year period. Of these requests, the Department of Pediatrics had the largest total number, or approximately 58 per cent. During the first ten of these 30 years it was estimated that about 75 to 80 percent of the requests for psychological services on in-patients came from the Department of Pediatrics, but apparently as other departments of the hospital became aware of the possible uses that they could make of such services, the number of requests from them increased.

Summary. These data indicate that in a sample of about 10,000 unselected patients examined in the Psychology Section of the Henry Ford Hospital, about twice as many children as adults were seen for psychological study during the period from 1926 to 1956. In addition to special psychological interviewing techniques, many different formal tests, totaling about forty-five, were used for purposes of supplementing diagnosis and planning definitive treatment or psychological counseling. Patients of all ages, from infancy to beyond eighty years, were seen, the median age of the entire group being approximately twelve years. These patients were classified into ten major psychological and psychiatric groups ranging from the normal to the disturbed and psychotic. A moderately normal distribution of intelligence was represented. Although the curve was skewed slightly toward the lower end of the scale, the range was from extreme mental deficiency to the exceptionally superior

levels, and the median IQ was within the low average range. The sources of referral to the Psychology Section included direct contact by the patients or their families, routine assignment by the Neuropsychiatric Division, and consultation requests from all other divisions of the Hospital, with the Department of Pediatrics issuing the majority of such requests.

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SCALENE LYMPH NODE BIOPSY

LEO J. KENNEY, M.D.*
CARLOS MOTA, M.D.,**

INTRODUCTION

Scalene lymph node biopsy is a simple operative procedure of great value in the diagnosis of intrathoracic disease. The anatomical basis for the operation is that the deep cervical lymph nodes anastomose freely with the mediastinal lymphatics. Any lesion that involves the mediastinal nodes may extend upwards into the cervical lymphatics. Hence, in many patients with obscure intrathoracic pathology a positive tissue diagnosis may be obtained by a minor operation performed under local anesthesia without resort to thoracotomy. It is to be emphasized that this discussion is NOT concerned with palpable lymph nodes in the neck.

INDICATIONS

Although the operation was described in 1949 by Daniel (1) it has not been utilized as frequently as it should in investigations of intrathoracic lesions. In general, the indications for the operation are three. FIRST, all patients with primary mediastinal lymphadenopathy should be given the benefit of the procedure as one of the early diagnostic steps. SECOND, in any case of pulmonary, esophageal or mediastinal malignancy of questionable resectability, a scalene node biopsy should be done. This is particularly important in patients with bronchogenic carcinoma who have mediastinal widening or if a barium swallow shows nodal indentation along the barium column. Involvement of the cervical lymph nodes with malignant tissue is considered a contra-indication to thoracotomy. THIRDLY, scalene lymph node biopsy is of particular value in patients who have diffuse pulmonary infiltrates not diagnosed by sputum studies, or other means. It is in this group that the percentage of positive results are high.

TECHNIQUE

The operative technique is as follows: The patient is placed in the supine position with the head turned to the opposite side from which the biopsy is to be done. A small pillow is placed under the shoulders to hyper-extend the neck. The skin is infiltrated with 1% procaine hydrochloride. An incision, five centimeters in length, is made one fingerbreadth above the clavicle with its mid-point between the clavicular and sternal heads of the sternocleidomastoid muscle (Fig. 1A) The dissection is carried through the platysma muscle down to the sternocleidomastoid muscle where the two heads are separated and retracted. The internal jugular vein is retracted medially and the deep cervical fascia beneath the vein is incised. The scalene fat pad will bulge through this incision and it is then picked up with an Allis forceps and carefully and completely removed from the surface of the anterior scalene muscle. (Fig.1 B and C). Now one can usually see the phrenic nerve and the transverse cervical artery on the surface of the muscle.

If the lymph nodes excised from the scalene fat pad do not contain grossly evident pathological changes, the operation is extended to other anatomical areas.

*Associate Surgeon, Division of Thoracic Surgery
**Surgical Resident, Division of Surgery

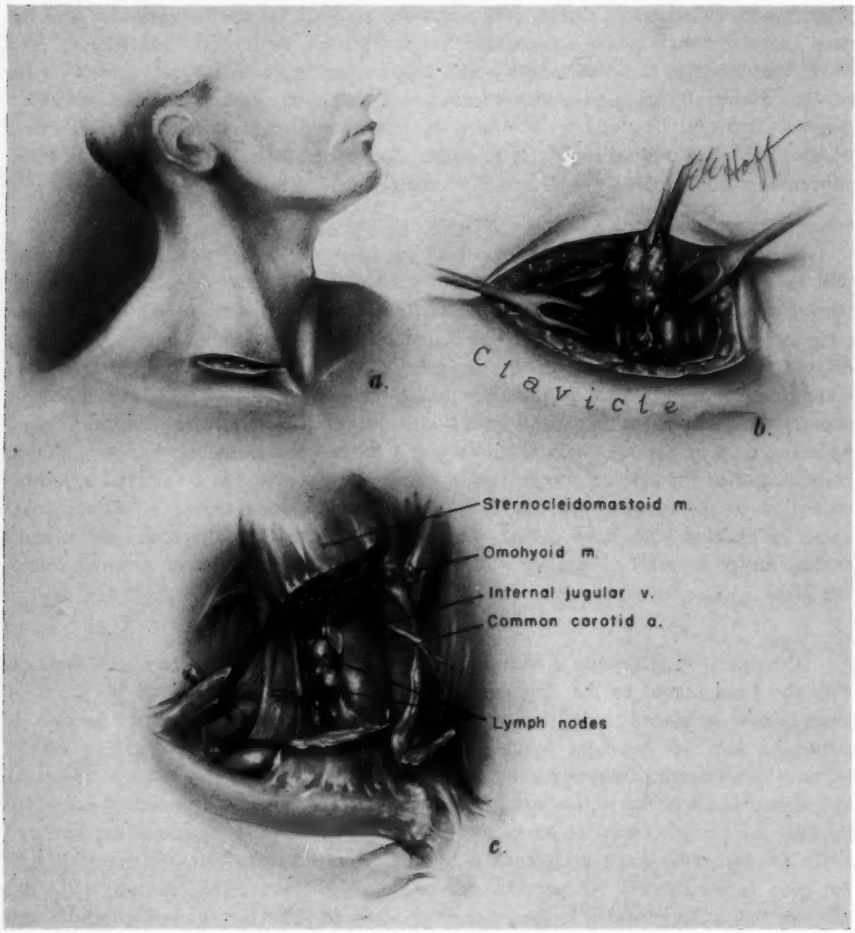

Figure 1

Illustration depicting the surgical technique of the scalene node biopsy. (A and B). Figure 1c shows a cut-away drawing of the anatomy of the scalene fossa. The phrenic nerve and the transverse cervical artery are shown on the surface of the scalenus anticus muscle.

Another mass of adipose tissue may be exposed beneath the clavicle. This mass lies directly upon the parietal pleura and has been a fruitful source of positive results when pulmonary lesions are present.

The carotid sheath can be mobilized and retracted laterally and it is then possible to explore the paratracheal region down into the mediastinum with blunt finger dissection. If enlarged lymph nodes are palpated in the mediastinum they may be biopsied with a sterilized laryngoscope and the laryngeal biopsy forceps. The wound is closed with interrupted silk sutures and the skin incision is covered with a protective layer of collodion.

Three to twelve lymph nodes may be removed from the fat pad (Fig. 2).

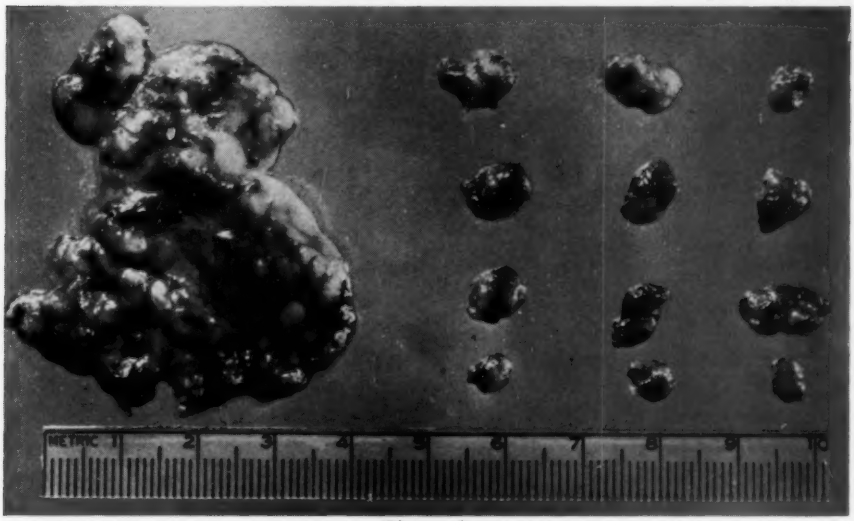

Figure 2

Photograph of a typical specimen of a scalene node biopsy. The fat pad is on the left. The lymph nodes on the right represent those excised from the fat and also several additional glands removed from the paratracheal area. Some of these lymph nodes contained large amounts of anthracotic pigment, a certain indication that an adequate dissection was carried out.

Frequently, positive nodes are reported microscopically when there was no gross evidence of pathology. This has been noted particularly in the Boeck's sarcoid cases. If the problem is one where infectious disease has to be considered in the differential diagnosis, half of the specimen is sent to the bacteriology laboratory for smears and cultures for fungus and tuberculosis, and the other half is submitted for routine pathologic studies.

SELECTION OF SIDE

The selection of the right or left sides for operation depends upon the particular problem under study. A bilateral procedure should usually be done in all patients with diffuse pulmonary infiltrates and also in those with primary mediastinal lymphadenopathy.

In pulmonary disease with unilateral lesions, the choice of side is based upon Rouviere's (5) description of the lymphatic drainage of human lungs. The right paratracheal lymph nodes drain the lymphatics of the right lung and, in addition,

Figure 3

Chest X-ray of a 65 year old man showing an atelectatic process involving the right lower and middle lobes. The superior mediastinum is widened to the right. The patient was hypertensive and had a moderate azotemia. A positive tissue diagnosis of undifferentiated carcinoma was established by right scalene node biopsy. The pulmonary lesion was considered inoperable.

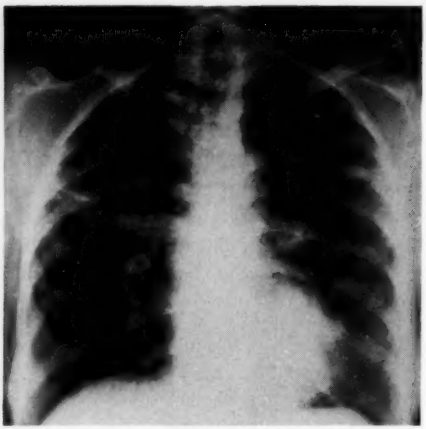

Figure 4

Photograph of a chest X-ray of a 65 year old woman showing diffuse bilateral pulmonary infiltrates. Extensive studies were carried out including bone X-rays, sputum studies for fungus and tuberculosis, cultures of bone marrow aspirate, blood chemistries, skin sensitivity tests and complement fixation tests on blood serum. A specific diagnosis could not be made. Bilateral scalene node biopsy was performed and a diagnosis of Boeck's sarcoid established. The positive nodes were found on the left side.

receive drainage from the left lower lobe via the sub-carinal plexus. The left upper lobe drains directly into the left paratracheal chain. Consequently, lesions involving any part of the right lung or the left lower lobe may be diagnosed by a right sided operation. In practice, we explore the right side first in all cases except the left upper lobe lesions. If obvious abnormal lymph nodes are not found, the left side is also dissected.

COMPLICATIONS

Complications resulting from the procedure are unusual, and in our series of 50 cases with 72 operations we have encountered no noteworthy complications.

Shefts (2) reports three instances of thoracic duct injury and one temporary Horner's syndrome in a total of 205 dissections. Harken (3) lists four complications in his 300 operations; two patients developed pneumothorax and hemorrhage occurred in two cases from injury to the internal jugular or subclavian veins. There have been no mortalities reported.

Table 1 COMPARISON OF INCIDENCE OF POSITIVE RESULTS IN SCALENE NODE BIOPSY

Author	Number of Cases	Positive Nodes	Percentage
Shefts (2)	187	67	35.8
Harkin (3)	142	45	31.7
Connar (4)	50	14	28
H. F. H.	50	15	30
Total	429	141	31.4

RESULTS

The results of scalene node biopsy are tabulated according to incidence of positive biopsies in Table I. Our figures, based on a group of 50 cases are compared with three other large series. The average yield of positive nodes in the composite group of 429 cases is 31.4%. This compares favorably with the results obtained in other diagnostic procedures, such as bronchoscopy in bronchogenic carcinoma where a positive tissue diagnosis can be expected in about 30% of the cases.

Table II

TYPES OF LESIONS DIAGNOSED BY SCALENE NODE BIOPSY
HENRY FORD HOSPITAL SERIES

	Cases
Boeck's Sarcoid	9
Bronchogenic Carcinoma	2
Carcinoma of the esophagus	1
Pulmonary Tuberculosis	2
Lymphoblastoma	1
Total	15

The types of pathological lesions diagnosed in our group of 50 cases is listed in Table II. It is noted that the incidence of positive results in Boeck's sarcoid is proportionately high. This is also true in Sheft's (2) series where of the 67 positive biopsies 38 of the cases were sarcoid. Scalene node biopsy should lead to a tissue diagnosis in at least half of the Boeck's sarcoid patients, a diesease process in which a specific diagnosis was seldom made previously by any means short of a thoracotomy. Several of these cases were considered to have pulmonary tuberculosis and had been confined to sanatoria and given long courses of therapy. The establishment of an accurate diagnosis was, of course, of inestimable benefit to these patients.

In addition to the diseases listed in Table II, that we found in our own series, others (2, 3, 4) have reported diagnosing metastatic tumors from the pancreas, kidney and cervix. The diagnosis of pulmonary lesions, such as histoplasmosis and silicosis, has been verified by scalene node biopsy. There are three instances recorded where the diagnosis of Hodgkin's disease was established.

CONCLUSIONS

This simple operation, performed under local anesthesia, is a very useful diagnostic tool in the evaluation of patients with intrathoracic disease. The procedure offers a method of establishing a positive tissue diagnosis in many cases that heretofore could only be diagnosed by thoracotomy.

In malignant lesions involving the lung, esophagus or mediastinum the resectability of the neoplasm can be assessed without resort to a major surgical exploration. If metastatic carcinoma is found in the scalene nodes, these patients are considered incurable by surgical means. Conversely, if the scalene node biopsy is negative, the surgeon is encouraged to procede with a radical excision of the lesion.

SUMMARY

The relatively new procedure of scalene node biopsy is described and the results of 50 operations are presented. The percentage of positive results in our series was 30%. The experience of the staff of the Henry Ford Hospital is compared with that of three other surgeons who have published papers on this subject.

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International Symposium

THE LEUKEMIAS: ETIOLOGY AND PATHOPHYSIOLOGY

March 8, 9, and 10, 1956

The professional staff of the Henry Ford Hospital with the initial advice and support of the Board of Trustees and Dr. Robin C. Buerki, Executive Director, of the Henry Ford Hospital, is sponsoring an international symposium on the subject The Leukemias: Etiology and Pathophysiology. This symposium will be held at the Henry Ford Hospital, March 8, 9, and 10, 1956, in the Clinic Auditorium. The preliminary program follows and has been prepared with the help of the advisory members.

Advisory Members:

Frank H. Bethell	The Thomas Henry Simpson Memorial Institute for Medical Research, Ann Arbor, Michigan
Sidney Farber	The Children's Hospital, Boston, Massachusetts
Howard R. Bierman	City of Hope Medical Center, Duarte, California
Joseph H. Burchenal	Memorial Center for Cancer and Allied Diseases, New York
Carl V. Moore	School of Medicine, Washington University, St. Louis, Missouri

Local Members:

John W. Rebuck, Chairman

Raymond W. Monto, Secretary

Wolf W. Zuelzer

PRELIMINARY PROGRAM

First Morning Session

8:50 A.M. Remarks of Welcome
Robin C. Buerki, Executive Director, Henry Ford Hospital

8:55 Announcements
John W. Rebuck

Chairman: *Wolf W. Zuelzer,* Detroit

The Leukemic Cell, Its Structure and Antigenicity

9:00 Electron Microscopy of Leukocytes
Marcel C. Bessis, Paris

9:30 Discussion Designated
Q. B. DeMarsh, Seattle

9:40 Phase Microscopy of Leukocytes
Sven Moeschlin, Solothurn, Switzerland

10:10 Discussion Designated
Oliver P. Jones, Buffalo

10:20 General Discussion

10:30 Intermission

10:40 Antigenicity of Leukocytic Fractions
Stuart C. Finch, New Haven

11:00 Leukocytic Agglutinins
John J. Butler, Rochester, N. Y.

11:20 Discussion Designated
James L. Tullis, Jamaica Plain, Mass.

11:30 General Discussion

12:30 Luncheon

First Afternoon Session

Chairman: *Howard R. Bierman,* Duarte, California

Genetic and Environment Factors in the Transmission of Leukemia

2:00 P.M. Lessons from Transplantation of Leukemia in Animals
Jacob Furth, Boston

2:20 Genetic and Non-Genetic Factors in the Induction of Leukemia
Arthur Kirschbaum, Houston

2:40 The Viral Etiology of Mouse Leukemia
Ludwik Gross, Bronx

3:00 Discussion Designated
Lloyd W. Law, Bethesda, Maryland

3:10 General Discussion

3:20 Intermission

3:30 Environmental Factors in Human Leukemia
L. J. Witts, Oxford, England

Radiation Biology of Leukocytes

4:00 Radiation Injury and Regeneration in Lymphoid Tissues
Henry S. Kaplan, San Francisco

4:20 Cytocidal Action of X-Rays on Lymphocytes According To Time-Lapse Cinemicrography and Unstained Cell Counts
Robert Schrek, Hines, Illinois

4:40 Discussion Designated
Leon O. Jacobson, Chicago

4:50 General Discussion

First Evening Session

6:30 P.M. Dinner — Hotel Statler

Chairman: *Carl V. Moore,* St. Louis

The Leukemias, Their Scope *Maurice N. Richter,* New York

The Malignant Lymphomas *Lawrence Berman,* Detroit

Second Morning Session

Chairman: *M. M. Wintrobe,* Salt Lake City, Utah

Leukocytic Physiology

9:00 A.M. Cultivation of Leukemic Cells in the Cartesian Diver
Jorgen Kieler, Copenhagen

9:30 Discussion Designated
E. E. Osgood, Portland, Ore.

9:40 General Discussion

9:50 Newer Concepts of Leukopoiesis as Revealed by Combined Leukophoretic and Isotopic Techniques
Charles G. Craddock, Jr., Fort Ord, California

10:10 Intermission

10:20 Endocrine Influences on Leukocytes
Albert S. Gordon, New York

10:40 Discussion Designated
Thomas F. Dougherty, Salt Lake City

10:50 General Discussion

11:00 Leukocytic Resistance
Edoardo Storti, Modena, Italy

11:30 General Discussion

12:30 Luncheon

Second Afternoon Session

Chairman: *L. J. Witts,* Oxford, England

Metabolism of Amino and Nucleic Acids in the Leukemias

2:00 P.M. Amino Acid Metabolism In Leukemia
H. Waisman, Madison, Wisconsin

2:20 Urinary Amino Acid Excretion in Leukemia
J. Awapara, Houston

2:40 The Free Amino Constituents of the Formed Elements of the Blood in Leukemia
George Rouser, Duarte, Calif.

3:00 General Discussion

3:10 Intermission

3:20 Metabolic Stability of PNA and DNA in Human Leukemic Leukocytes and the Function of Lymphocytes
L. D. Hamilton, New York

3:40 Urinary Uric Acid and Non Uric Acid Purine Excretion in Leukemia
I. Krakoff, New York

4:00 Nuclease Inhibitors
R. W. Vilter, Cincinnati

4:20 Studies on Cysteine Metabolism in Leukemia
A. S. Weisberger, Cleveland

4:40 General Discussion

Second Evening Session

8:00 P.M. Round Table—Henry Ford Hospital Auditorium

Present Status of New Clinical Agents and Combinations in Treatment of the Leukemias

Chairman: *Frank H. Bethell*, Ann Arbor

Joseph H. Burchenal, New York
Sidney Farber, Boston
William Dameshek, Boston
A. Gellhorn, New York
C. A. Doan, Columbus
Joseph M. Hill, Dallas
M. M. Wintrobe, Salt Lake City

Third Morning Session

Chairman: *Sidney Farber*, Boston

Further Biochemical Considerations in the Leukemias

9:00 A.M. Immunologic Studies of Protein Synthesis in Leukemia
H. C. Hopps, Oklahoma City

9:20 Biochemical and Enzymatic Characteristics of Normal and Leukemic Leukocytes
W. N. Valentine, Los Angeles

9:40 Metabolism of PGA and CF in Leukemic Cells
R. R. Ellison, New York

10:00 Designated Discussion
R. J. Rossiter, London Ont., Canada

10:10 General Discussion

10:20 Intermission

10:30 Lactic Acid Production By the Human Polymorphonuclear Leukocyte
S. P. Martin, Durham, N.C.

10:50 General Discussion

11:00 Diagnostic and Nosological Problems at the Borderline of Leukemia
F. G. J. Hayhoe, Cambridge, England

11:30 General Discussion

12:30 Luncheon

Third Afternoon Session

Chairman: *Joseph H. Burchenal*

Memorial Center for Cancer and Allied Diseases, New York

Nucleic Acids as the Target for Chemotherapy: Mechanisms of Drug Action and Resistance

2:00 P.M. The Specific Action of Azaserine and Other Anti-Carcinogens on Enzymes Concerned with Purine Biosynthesis
John M. Buchanan, Cambridge, Mass.

2:20 Biosynthesis of Nucleic Acids and Neoplasia
David A. Goldthwait, Cleveland

2:40 Nucleic Acids and Related Derivatives as Targets for Chemotherapy
George B. Brown, New York

3:00 Studies on Resistance to Folic Acid Antagonists
Charles Nichol, New Haven

3:20 General Discussion

3:30 Intermission

3:40 Nutritional and Metabolic Variations in Drug Resistant Bacteria
Dorris J. Hutchison, New York

4:00 Nucleotide Metabolism and Cancer Chemotherapy
Howard E. Skipper, Birmingham, Ala.

4:20 Antagonists of Nucleic Acid Derivatives
George Hitchings, Tuckahoe, New York

4:40 Anti-Cancer Agents and Nucleic Acid Metabolism of Isolated Human Leukocytes
Richard J. Winzler, Chicago

5:00 General Discussion

INTRODUCTION TO NEW STAFF PERSONNEL

Many new professional staff positions have been created recently in addition to the few periodically being vacated for one reason or another. Many of the new staff physicians coming to the hospital immediately go to work in an isolated division or laboratory and several months elapse before the rest of the staff is aware of their arrival. For this reason, beginning with this issue, the bulletin will carry a brief biographical sketch of all new professional personnel joining the staff.

ROBERT C. HORN, JR., M.D., came to us September 6, 1955, and officially became Director of Laboratories October 1, 1955. He is a native of Allentown, Pennsylvania, and is 42 years of age. He took his undergraduate work at Muhlenberg College and received his M.D. degree from Yale in 1937. He interned in Danville, Pennsylvania, and then took his complete Pathology Residency at Presbyterian Hospital in New York City. He belongs to the Wayne County Medical Society, American Medical Association, American Association of Pathologists and Bacteriologists, American Society of Clinical Pathologists, College of American Pathologists, International Academy of Pathologists and American Association of Cancer Research. Prior to coming here, he spent 13 years as the Professor of Surgical Pathology at the University of Pennsylvania Medical School Hospital. He is married with 3 children and resides at 505 Pemberton Road in Grosse Pointe.

MARK S. BEAUBIEN, M.D., returned to our staff in Medical Clinic No. 2 on November 1, 1955. He is a native of Chicago and is 34 years of age. He graduated from the University of Chicago in 1943 and received his M.D. degree from the same school in 1946. He interned at Gorgas Hospital, Ancon, Canal Zone, and took his 3 year residency in Internal Medicine at the Presbyterian Hospital in Chicago. He then spent 2 years in private practice in Lansing, Michigan, before coming here for one year in 1952. He has spent the last 2 years in the U. S. Army. He is married with 3 children and resides at 460 S. Glenhurst in Birmingham.

JAMES M. COLVILLE, M.D., joined our staff in the Infectious Disease Clinic on July 1, 1955. He is a native of Detroit and is 31 years of age. He graduated from Michigan State College and received his M.D. degree from Cornell University in New York City in 1948. He interned and took 2 years of Medical Residency at New York Hospital. He then took his last year of residency at the University of Oklahoma. He spent 1 year as a Research Fellow for the National Infantile Paralysis Foundation at the University of Rochester. He is a member of Alpha Omega Alpha and the American Federation of Clinical Research. He is a veteran of World War II. Dr. Colville is married with 2 children and resides at 1802 Houstonia Street in Royal Oak.

VOLCKHERDT M. deGROOT, M.D., came to us July 1, 1955 to join our Ophthalmology Staff. He is a native of Haarlem, The Netherlands, and is 30 years of age. He received his M.D. degree from the University of Amsterdam in 1951. He interned in Valhalla, N. Y. and Baltimore. He then took his 3 year Ophthalmology Residency at the Wilmer Institute, Johns Hopkins University Hospital. He is married and resides at 3541 Oakshire in Berkley.

WILLIAM S. HAUBRICH, M.D., joined our staff in Gastroenterology on July 13, 1955. He is a native of Columbus, Ohio, and is 32 years of age. He graduated from Franklin and Marshall in 1943 and received his M.D. degree from Western Reserve University in 1947. He interned at the Graduate Hospital, University of Pennsylvania in Philadelphia. He took a 1 year residency in Pathology and a 2 year residency in Internal Medicine at the Cleveland City Hospital from 1948 to 1951. He then took 1 year of Gastroenterology at the Graduate Hospital, University of Pennsylvania, following which he spent 1 year in private practice at Lakewood, Ohio. Dr. Haubrich then was Chief of the Gastroenterology Service, Madigan Army Hospital, Tacoma, Washington, from 1953 to 1955. He is married with 1 child and resides at 270 South York Street in Dearborn.

WILLIAM J. HOPKINS, M.D., joined our Urology Staff on January 1, 1956. He is a native of Blencoe, Iowa, and is 40 years of age. He graduated from Creighton University in 1943 and received his M.D. degree from the same University in 1944. He interned at Creighton Memorial Hospital in Omaha and then took his entire residency training in Pathology, General Surgery and Urology at Johns Hopkins from 1947 to 1954. For the past 1½ years, he has been Assistant Professor of Urology at Johns Hopkins. He is a veteran of World War II, is married and resides at 16626 Fairfield in Detroit.

JAMES E. LADD, M.D., joined our staff in Obstetrics and Gynecology on December 1, 1955. He is a native of Abbeville, S. C., and is 31 years of age. He graduated in 1947 from Franklin and Marshall and received his M.D. degree from Temple University in 1951. He interned and took his complete residency training at Temple. He is a veteran of World War II. He is married with 2 children and resides at 22505 Nona in Dearborn.

GORDON MANSON, M.D., joined our Pediatric Staff on July 5, 1955. He is a native of Burlington, Vermont, and is 33 years of age. He graduated in 1948 from the University of Kansas and received his M.D. degree from the University of Vermont in 1952. He interned at the Iowa Methodist Hospital in Des Moines, and then took his complete Pediatric Residency at the Raymond Blank Memorial Hospital for Children in Des Moines. Dr. Manson is a veteran of World War II. He is married with 2 children and resides at 17563 Rutherford Avenue.

WALLACE McWHIRTER, M.D., joined our Radiology Staff on August 10, 1955. He is a native of Roff, Oklahoma, and is 36 years of age. He graduated from the University of Oklahoma in 1947 and received his M.D. degree from the same school in 1951. He interned at Mercy Hospital in Oklahoma City and took his Radiology Residency at Grace Hospital in Detroit. Dr. McWhirter is a veteran of World War II. He is married with 1 child and resides at 10863 Nottingham in Detroit.

ROBERT SCHOPBACK, M.D., joined our Department of Neurology and Psychiatry on September 26, 1955. He is a native of Philadelphia and is 36 years of age. He attended Drexel Institute of Technology and Temple University for his undergraduate training and received his M.D. degree from Jefferson Medical School in 1944. He took his Psychiatry Residency with the VA Deans Committee in Philadelphia from 1947 to 1949. He then was head of the Psychiatry Department at Clifton Springs, N. Y. until he came here. He was vice-president of the Finger Lakes Neuro-Psychiatry Society. He is a Fellow of the American Psychiatric Association and a delegate to the convention of the APA. He is married with 1 child and resides at 284 Fisher Road in Grosse Pointe Farms.

JOSEPH C. SIERACKI, M.D., returned to our Pathology Staff on December 2, 1955. He is a native of Dickson City, Pennsylvania, and is 30 years of age. He graduated from the University of Pennsylvania in 1947 and received his M.D. degree from the University of Buffalo in 1951. He interned at Henry Ford Hospital and took 2 years of Pathology Residency here. Dr. Sieracki then spent 1½ years at the Cancer Research Institute, New England Deaconess Hospital in Boston. He is married with 1 child and resides at 4844 Lakewood in Detroit.

DONALD STRATTON, M.D., joined our Radiology Staff on August 10, 1955. He is a native of Aylmer, Ontario, and is 28 years of age. He graduated from Wayne University in 1948 and received his M.D. degree from the same school in 1951. He interned at Highland Park Hospital and then took his complete Radiology Residency at Harper Hospital. He is married and resides at 118 W. Grand Avenue in Detroit.

JOYCE WHITE, M.D., joined our staff in the Otology Research Laboratory on December 5, 1955. She is a native of Winnipeg, Manitoba, Canada. Dr. White graduated from the University of Chicago in 1943 and received her M.D. degree from the same school in 1953. From October 1942 to September, 1943, she was an assistant in the Department of Physiology, University of Chicago, and Night Anesthetist at Chicago Lying In Hospital. From October, 1944 to June, 1952, she was the Chief Tester in the Biological Psychology Laboratory of the University of

Chicago. From January, 1954 to November, 1955, she was Supervisor of the Diagnostic Control Section of Michigan Hospital Service. She is a member of the Association of Medical History. She is married and resides at 1339 Hampton in Grosse Pointe Woods.

FRED W. WHITEHOUSE, M.D., returned to our staff in the Metabolism Clinic on October 1, 1955. He is a native of Chicago and is 29 years of age. Dr. Whitehouse graduated from Northwestern University and received his M.D. degree from the University of Illinois in 1949. He interned at Henry Ford Hospital and then spent 2 years as a U.S. Navy Flight Surgeon. He spent 2 years as a Medical Resident at HFH and then 1 year as a Fellow in Medicine at New England Deaconess Hospital in Boston where he worked with Dr. Joslin. He is a member of the American Diabetes Association. He is married with 2 children and resides at 19639 Cardoni in Detroit.

IRENE T. KLINE, Ph.D., joined us December 1, 1955, as a Research Associate in the Division of Endocrinology and in the Department of Biochemistry of the Edsel B. Ford Institute. She is a native of Harmony, N. Y., and is 46 years of age. She graduated from Oberlin College in 1931, received her M.A. degree from Duke University in 1941, and obtained her Ph.D. from Western Reserve in 1950. In 1951, she was an instructor in the Department of Medicine at Yale University School of Medicine. Since then she has been Assistant Professor in Biochemistry and Obstetrics-Gynecology at Western Reserve University School of Medicine. Dr. Kline is a member of the Sigma Xi Fraternity, New York Academy of Sciences, American Association for the Advancement of Science, American College of Scientists and the American Endocrine Society. She resides at 7702 E. Jefferson in Detroit.

VINCENT MASSEY, Ph.D., joined our Biochemistry Staff on October 13, 1955. He is a native of Unanderra, N.S.W., Australia, and is 29 years of age. He received his B.S. degree from the University of Sydney in 1947 and his Ph.D. from Cambridge University in 1953. He worked in the Biochemistry Department at the University of Cambridge before coming here. Dr. Massey is a member of the Biochemistry Society of London, England. He is married with 1 child and resides at 12635 Outer Drive.

ABSTRACTS OF RECENT PUBLICATIONS OF THE PROFESSIONAL STAFF OF THE HENRY FORD HOSPITAL AND THE EDSEL B. FORD INSTITUTE FOR MEDICAL RESEARCH

NOBLE PLICATION OPERATION FOR CHRONIC RECURRING INTESTINAL OBSTRUCTION. J. BARRON AND L. S. FALLIS. A.M.A. Arch. Surg. 71:518, 1955.

The Noble plication operation for controlling peritoneal adhesions in chronic recurring intestinal obstruction has definite value. The operation should be carried out as a planned procedure after careful preparation of the patient, with special emphasis on the nutritional deficiency. The best results are obtained when the entire jejunum and ileum are plicated. Failures result from limited application of the technique. The dependent completely plicated jejunum and ileum may produce duodenal ileus. The prevention and treatment of this complication is discussed.

DILEMMA OF GASTRIC ULCER—BENIGN OR MALIGNANT? B. E. BRUSH AND R. J. PRIEST, J. Am. Geriatrics Soc. 3:1027, 1955.

Gastric ulceration in the geriatric patient should be considered as an individual problem in differential diagnosis between cancer and a benign ulcer. Diagnostic procedures for complete evaluation of a patient with gastric ulceration are reviewed. Precise indications for prompt operative measures are outlined. A trial of medical therapy in the hospital is recommended for those patients in whom the initial evaluation is reassuring. When progress studies fail to demonstrate complete healing in from four to six weeks, prompt surgical intervention is recommended. The physician must assume responsibility for the recall of the patient for these studies. It is mandatory at regular intervals to reevaluate the patients in whom ulcers have healed completely under medical management.

SMALL INTESTINAL RUPTURE FROM NON-PENETRATING ABDOMINAL TRAUMA. T. GEOGHEGAN, E. J. GORDON, AND B. E. BRUSH. J. Michigan M. Soc. 54:1223, 1955.

In this review of nineteen cases of perforation of the intestine from non-penetrating trauma jejunal and ileal perforations comprise the bulk of the lesions with the jejunal perforations having twice the mortality of the ileal perforations. No instances of gastric or colon perforations were encountered. Most of the cases resulted from industrial accidents. Prompt surgical therapy with closure of the opening in the bowel remains the single most important factor in restoring the patient to health. Exploration on suspicion is warranted to avoid death or prolonged morbidity. In addition to blood and fluid replacement, long tube suction and antibiotics are important adjuvants in the preoperative and postoperative treatment. These innovations have improved the

prognosis for patients with this type of injury. The mechanism of rupture of the intestine with an intact abdominal wall is thought to be bursting of the intestine due to increased intraluminal pressure rather than direct crushing of the bowel.

RATIONAL MANAGEMENT OF ACUTE PANCREATITIS. W. S. HAUBRICH. Ohio M. J. 51:1085, 1955.

Effective management of acute pancreatitis begins with prompt recognition of the disease. This implies detection of elevation in serum pancreatic enzymes by the alert physician. Although the nature of the initial insult to the acinar cells of the pancreas remains in controversy, the pathologic physiology dictates a rational plan of treatment which includes: a) correction of shock b) control of pain and c) "pancreatic rest". Practical measures implementing this triple approach are described. In convalescence the case can be satisfactorily completed only by pursuing appropriate studies to uncover an underlying cause and to detect early complication requiring further definitive treatment.

CARCINOMA OF THE STOMACH. R. C. HORN. Gastroenterology 29:515, 1955.

Seventy-four cases of gastric carcinoma studied at autopsy in the Hospital of the University of Pennsylvania since 1942 have been reviewed. Although 17.6% (10 cases) of the 57 tumors for which gastric resection was not done were localized to the stomach and its immediate vicinity and could have been considered "theoretically curable," only two should really be so classified after careful restudy. These were incidental findings in patients dying of unrelated disease. In 14 cases without symptoms suggesting gastric disease, the diagnosis was not made until autopsy. Only two of these tumors—the same two noted above—were localized and in a theoretically treatable state. There is thus no valid evidence that a significant number of gastric cancers are coming to autopsy in a state presenting a good opportunity for surgical cure. There is abundant evidence that gastric cancer may be silent, so far as local symptoms are concerned, even when it has metastasized widely. Among 17 autopsies on patients who underwent gastric resection, there were 9 patients who survived resection for 5 weeks to 27 months. All had widespread metastases at autopsy, six without local disease. Among the 8 patients who died in the postoperative period, 4 had residual tumor, all with distant spread. The likelihood that dissemination usually occurs early in the disease and not from local recurrences is strenghtened by the observation that in 266 cases of gastric cancer explored surgically, distant metastasis, with or without local spread outside the stomach, was found in 89 (33.5%) at the time of exploration. More extensive surgical procedures than conventional subtotal gastric resection may well be applicable in selected cases but it does not seem reasonable to expect them to effect a significant reduction in the mortality from gastric cancer.

INDUCED CARDIAC ARREST FOR INTRACARDIAC SURGICAL PROCEDURES. C. R. LAM, T. GEOGHEGAN, AND A. LEPORE. J. Thoracic Surg. 30:620, 1955.

In order to accomplish certain cardiac operations, a method must be devised to stop the heart for a period of time and then restart it at will. For example, grafting procedures on the coronary arteries, and direct vision surgery of the aortic valve are probably impossible to perform on the beating heart. If the heart continues to beat while the coronary flow is interrupted, the discrepency between myocardial blood supply and muscular activity impedes recovery of the heart. A method was developed of suddenly stopping the normally beating heart which was consistent and reversible. A 5 per cent solution of potassium chloride is injected into the left ventricular cavity while the ascending aorta is compressed. The solution enters the coronary arteries causing cardiac arrest in about 30 seconds. The still heart may be manipulated or incised. Following completion of the surgical procedure the heart beat is restored by simple massage. A phase of coarse ventricular fibrillation usually ensues. Countershock converts this to regular rhythm. Cardiac arrest for 30 minutes was induced in 20 dogs which had right atrial cardiotomies during hypothermia of 22° C. Seventeen of these animals survived the operative procedure and 15 of them survived without cardiac or neurological abnormalities for a week or more. These results were not materially different from those in a control series of 30 animals in which ventricular fibrillation was induced or the heart beat was not deliberately altered during 30 minutes of circulatory occlusion at 22° C.

CLINICAL INVESTIGATION IN DERMATOLOGY. C. S. LIVINGOOD. J. Invest. Dermat. 25:203, 1955.

A successful clinical investigative study must be planned so that the design of the experiment will make certain that the maximum information is obtained with a minimum of effort. The beginner as well as the experienced clinical investigator should not embark on any project without preparing an outline of the factors which may produce a result and the possible answers which experimental approach will yield. One of the many pitfalls to avoid in planning a clinical investigative project is an attempt to evaluate several variables in the same experiment. Some of the factors which must be considered in planning a controlled clinical study when we wish to evaluate an orally or parenterally administered therapeutic agent include the sex, age, economic status, occupation, severity of the disease, and the presence or absence of complications. For example, one fundamental consideration in conducting a valid controlled therapeutic study of two samples of patients with herpes zoster is the age factor. Clinical investigation has had an important role in the development of our specialty. Clinical dermatologists as a group have the spirit of inquiry. They have used the laboratory when it is applicable to the problem at hand—recall the

work which has been done by some of our colleagues in the field of fungus infections. Some of the future advances in our specialty will continue to be made by clinical researchers. This Society should have a part in this, and it could be done by encouraging the presentation of a representative number of papers dealing with clinical investigation at these meetings.

OBSERVATIONS ON THE MECHANISM OF INTRANASAL ABSORPTION OF VITAMIN B_{12} IN PERNICIOUS ANEMIA. R. W. Monto and J. W. Rebuck. Blood 10:1151, 1955.

Two patients with classical clinical and hematological findings of pernicious anemia were treated by single applications of crystalline vitamin B_{12} on the nasal mucous membranes in amounts of 150 and 200 mcg. respectively. Completely clinical and hematological remissions followed which lasted two to four months. Both patients demonstrated maximum reticulocytosis. In one patient nasal washings obtained after application of vitamin B_{12} to a normal subject were introduced into the stomach via a tube. In a ten-day period of observation there was no increase in reticulocyte count. It is concluded that crystalline vitamin B_{12} is absorbed directly from the nasal mucous membranes without binding or combining with "intrinsic factor". This form of therapy has the advantage of the economy of time and cost to the patient. Chronic disease of the nose did not contraindicate this form of therapy. Local irritation of the mucous membranes by crystalline B_{12} or the vehicles employed has not been observed.

CLINICAL EVALUATION OF HYDROCORTISONE OINTMENT. J. Fred Mullins and E. M. Shapiro. GP 12:59, 1955.

Three hundred patients representing a variety of inflammatory dermatoses were treated by local application of hydrocortisone acetate or hydrocortisone free alcohol. Concentrations of 1 per cent and 2½ per cent were used in a vanishing cream base. Results generally were good. Dermatosis in thin-skinned areas was especially responsive. Relief was almost instantaneous for patients having pruritus of the anus, vulva or scrotum. Hydrocortisone ointment is not a panacea. However, it may make the patient comfortable while other specific measures are brought into use.

AMOUNT OF TISSUE TO BE PRESERVED AT SUBTOTAL THYROIDECTOMY: AN ESTIMATE BASED ON SERIAL ISOTOPE TRACER MEASUREMENTS. D. E. Szilagyi, J. L. Barrett, and L. E. Preuss. J. Clin. Endocrinol. 15:1409, 1955.

The optimum amount of thyroid parenchyma to be left in situ when thyroidectomy is performed for nonmalignant disease would, by definition, be the amount that will assure postoperative euthyroidism and reduce to a minimum the likelihood of recurrence. In practice, this is the smallest quantity compatible with a euthyroid state. A knowledge of this amount is of obvious importance, and hitherto it has been

estimated largely by empirical guessing. Hence, during a period of two years, we have attempted to measure it quantitatively by studying the postoperative functional state of thyroid remnants in a series of 25 cases of subtotal thyroidectomy performed in comparable groups of diffuse hyperplastic, toxic nodular and nontoxic nodular goiter. The extent of the operation was controlled by careful measurement of the tissue remnant by a matched-weight method. Postoperatively, all replacement medication was withheld and at intervals of three to six months tracer doses of radioiodine (I^{131}) were administered. The uptake of the isotope in the thyroid area and, in some cases, its excretion in the urine were determined as primary indices of the functional capacity of the remaining thyroid parenchyma. The relationship between the functional capacity of the thyroid remnant and other laboratory indices of thyroid activity such as the basal metabolic rate and the level of serum protein-bound iodine and cholesterol was also studied. The tissue remnant showed functional growth in most instances, the only exceptions being tissue rests of exceedingly small size (less than 150 mg.) or of hypoplastic histologic structure. The minimal amount of thyroid tissue to be spared for the maintenance of euthyroidism was found to be much less than hitherto assumed, namely about 0.8 Gm. in diffuse hyperplastic goiter, and about 1.0 Gm. in toxic nodular goiter. Observations over several more years are necessary in order to determine whether operations designed to spare only these small amounts of thyroid parenchyma will be followed by a significantly lower incidence of recurrent goiter. The very small size of the optimal thyroid remnant places new emphasis on the need for an anatomic thyroidectomy. Such small pieces of parenchyma cannot be safely dissected out without complete topographic definition of the thyroid gland and careful identification of the recurrent laryngeal nerve and parathyroid bodies.

HEMANGIOENDOTHELIOMA OF LIVER FOLLOWING THORIUM DIOXIDE ADMINISTRATION. H. Tesluk and W. A. Nordin. A.M.A. Arch. Path. 60:493, 1955.

Thorium dioxide (Thorotrast) by virtue of its radioactivity has the potentiality of producing neoplastic change in man. Although such cases are rare, most patients receiving the material have not provided a sufficient time of exposure, since the latent period is longer than 10 years. A case is presented in which hermangioendotheliomatous lesions were encountered in the liver of a patient given thorium dioxide 14 years previously. Thorium dioxide-induced neoplasms in the literature include two similar cases.